UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: VALSARTAN PRODUCTS LIABILITY LITIGATION

CIVIL ACTION NUMBER: 19-md-02875-RBK-KMW

EVIDENTIARY HEARING via ZOOM TELECONFERENCE

Mitchell H. Cohen Building & U.S. Courthouse
4th & Cooper Streets
Camden, New Jersey 08101
March 2, 2022
Commencing at 9:32 a.m.

B E F O R E: **THE HONORABLE ROBERT B. KUGLER**
UNITED STATES DISTRICT JUDGE

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Larry MacStravic, Courtroom Deputy

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I N D E X

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E X A M I N A T I O N S

(PROCEEDINGS held via Zoom before The Honorable ROBERT B. KUGLER at 9:30 a.m.)

THE COURT: Well, I think we're all here. And good morning, everybody. As you know, I'm Judge Kugler.

What we need to do this morning is set some ground rules.

The first is, if you're not participating, we would appreciate if you would go off the video, because we have a lot of people on the screen, and we have a court reporter who is trying to figure out who is saying what to whom.

The second thing is, I need you to identify now, for us, who is going to do the questioning of the witness, and who, on the odd chance there might be an objection, will be speaking on behalf of the plaintiff.

So who is going to be doing the questioning?

MS. LOCKARD: Your Honor, Victoria Lockard.

THE COURT: Ms. Lockard, you have some feedback going on big time.

MS. LOCKARD: I understand. Our tech is taking care of that in the room.

THE COURT: Okay. In fact, I barely heard what you said, Ms. Lockard.

Are you doing the questioning or --

MS. LOCKARD: Yes, Your Honor. I'll be doing the questioning.

THE COURT: And then who will be speaking on behalf of the plaintiff, if it's necessary to raise any objections?

MR. SLATER: Good morning, Your Honor, Adam Slater for the plaintiffs. I'll be, quote/unquote, defending Dr. Lagana at the hearing.

THE COURT: Okay.

MS. BROWN: Good morning, Your Honor. This is Alli Brown, and I'll be doing the questioning for Dr. Etminan later today.

THE COURT: Okay.

MS. BROWN: Thank you.

THE COURT: By the way, did we work out the timing later today? I know one of the counsel had a potential conflict with another case.

MS. BROWN: It was me, Your Honor. And we're hopeful that if necessary, I understand the plaintiffs are amenable to -- with the Court's permission, a short 30-minute recess at 2:00 if we are in the middle of the questioning.

THE COURT: Sure.

MS. BROWN: Thank you, Your Honor.

THE COURT: No problem.

THE COURT: Mr. Trischler, how are you? You wanted to say something.

MR. TRISCHLER: I was just going to finish if the Court wanted the full game plan for today.

I will be doing the questioning of Dr. Panigrahy.

THE COURT: He's next, as I understand it. Correct?

MS. BROWN: I believe that's the order, yes, sir.

MR. SLATER: Correct.

THE COURT: Mr. Slater, are you going to, quote, defend that one also?

MR. SLATER: I am not going to. That will be I think Mr. Nigh.

MR. NIGH: That's correct. That would be me, Your Honor, Daniel Nigh.

THE COURT: Then why don't we get started with Dr. Lagana.

Dr. Lagana, I see you on here. Would you raise your right hand.

THE WITNESS: Yes, sir.

STEPHEN LAGANA, MD, PLAINTIFFS' WITNESS, after being duly sworn, was examined and testified as follows:

THE COURT: State your full name.

THE WITNESS: Stephen Michael Lagana.

THE COURT: All right, Ms. Lockard. He's all yours.

DIRECT EXAMINATION

BY MS. LOCKARD:

Q. Good morning, Dr. Lagana.

A. Good morning.

Q. You and I haven't had an occasion to meet quite yet, have

we?
A. Not to my knowledge.
Q. Last week you submitted a certification in further support of your general causation opinions in this case. Correct?
A. Correct.
Q. And that was dated February 23, 2022. Correct?
Do you have that in front of you?
A. I do.
Q. Just --
A. Yes, that is the correct date.
Q. All right. And did you draft that certification yourself?
A. No.
Q. Okay. So you didn't write that certification, the lawyers did?
A. The lawyers drafted it with my input. We discussed everything in it in great detail, and they transcribed my thoughts.
Q. Now, you understand we're not here today to discuss the challenges defendants have made as to your qualifications as a pathologist. Do you understand that?
A. That's my understanding, yep.
Q. And is it your understanding that one of the reasons we're here today is to discuss the challenges defendants have

made to your methodology in arriving at your conclusions?
A. Correct.
Q. And your methodology in this case was to evaluate and take into account the various categories of medical and scientific literature and evidence discussed in your report and in your deposition. Correct?
A. Yes. As I stated, I applied a weight of evidence methodology and applied the guidelines of Sir Bradford Hill.
Q. Exactly. And so essentially what you did in terms of your methodology is you applied Bradford Hill, you did a weight of the evidence analysis, you did a research project, and you looked at the articles and literature that were generated based on your research and rendered opinions based on those -- that research alone. Correct?
A. I think that what you just described gets to the -- gets to the essence of what I did.
Q. Now, just for background, you are an anatomic pathologist. Correct?
A. Correct.
Q. You spend 75 percent of your time on clinical commitments and reviews of specimens. Right?
A. Correct.
Q. And your professional time, when you're not doing legal work like today, is first and foremost clinical work, then administrative, which has continued to increase, then teaching

and then research?

A. Absolutely not.

MR. SLATER: I'm sorry, Your Honor. I'm very hesitant to object, because I do understand what Your Honor said earlier. I don't -- and I certainly don't want to disrupt. I'm just concerned that we're not within the parameters Your Honor set.

MS. LOCKARD: Your Honor, if I may, Dr. Lagana, he has set forth a methodology in this case that defendants have challenged as being outside of his normal expertise and practice in the scope of his duties.

I'm not challenging -- we are not challenging or getting into his background credentials and qualifications, how many papers he's written and that sort of thing. But when this Court gave us the parameters at this hearing, the Judge -- you were very specific. You said, we need to know if this is something that the witness does outside of litigation, and if there wasn't litigation or compensation involved, that he would apply the very same methodology that he has applied in this case.

So I am not getting into his background, but I do think we have a need -- a fair opportunity to get into his methodology and how it differs from his normal work.

THE COURT: How is this any different from what you raised in your motion?

MS. LOCKARD: Well, it is -- there are certainly questions in -- issues in the motion that bear on this which is why we are trying to get this testimony in the record today to support the arguments that we made in our motion.

THE COURT: Well, you cited extensively to his deposition testimony in your motion papers. I'm well aware of the fact that you assert that he does not follow the same methodology he follows in his normal daily activities as a pathologist. I get that. Really, I do.

The point of this is really the question about what he put in his certification. So let's -- I mean, I'm going to give you some leeway to get some background information done, but let's please focus on his certification. Okay?

Thank you.

MS. LOCKARD: Understood, Your Honor. We'll move forward.

BY MS. LOCKARD:

Q. In terms of your certification, you make reference in it to a differential diagnosis. Correct?

A. Correct.

Q. And in your practice as a pathologist, you can and frequently do diagnose cancers without giving an etiology of the cancer. True?

A. You know, in a general sense, it's not always required to provide an etiology, but there are certainly plenty of

examples, not terribly rare examples, in which providing an etiology is absolutely expected of an anatomic pathologist. So there's no real blanket answer to that. It's sometimes yes and sometimes no. It depends if it's clinically useful or not.

Q. Well, the truth of the matter, Dr. Lagana, is that the etiology of a cancer essentially never goes into your report. Isn't that right?

A. No, that's not right. No.

Q. Do you have a copy of your deposition with you?

A. Uh-huh.

Q. And we can pull that into the chat feature potentially if we have that access of others.

MS. LOCKARD: But Your Honor, may I read from Dr. Lagana's deposition?

MR. SLATER: We'd just request that the pages and lines be identified so that we can all get to those first.

MS. LOCKARD: Sure.

THE COURT: I would like to -- give us a page, please.

BY MS. LOCKARD:

Q. Absolutely. Turn to page 80, Dr. Lagana, line 15.

A. Sure.

Q. Let me know when you're there.

A. Uh-huh.

Q. When my partner, Ms. Cohen, was deposing you in your sworn deposition back on August of 2021, you were asked the question at line 15: Have you ever used those words in a report?

And your response, line 17, was, and I'll read: The etiology of a cancer essentially never goes into a report.

Did I read that correctly?

A. Yep.

Q. And so even if you diagnose a lung cancer, you don't say lung adenocarcinoma, smoking related. You just put lung adenocarcinoma. True?

A. For lung adenocarcinoma, that's true. And when I answered the question previously, I stated that there are some cancers in which the etiology is clinically relevant and expected that a pathologist will include it, and there are some that it is not.

So lung cancer for the most part is an example where the etiology is assumed in most cases and the pathologist would not include that in a report.

And I am aware of the testimony that I gave, that you cited. And in looking back on it, it was inartful.

And I think if we look at further testimony, specifically on page 87, when Ms. Cohen continued -- I'm sorry, I'm still answering.

Am I allowed to finish my answer?

Q. I would like for you to answer the question. I understand there's no direct testimony allowed. And I think you have answered my question, Dr. Lagana.

THE COURT: Ms. Lockard, you need to let the witness finish. And if you don't think it's responsive, if you need the assistance of the Court, you can ask for the Court's assistance, but we have to let the witnesses finish their testimony. Okay? Thank you.

MS. LOCKARD: Understood.

BY MS. LOCKARD:

Q. Go ahead, Doctor.

A. Thank you. As the questioning in my deposition continued, examples came to my mind where actually it is very important for an etiology to be included in a report. And I brought those out during deposition, specifically on page 87 where I talk about the need to identify human papillomavirus related to cancers of the oral cavity as opposed to smoking-related cancers of the oral cavity. And the reason for that is because the human papillomavirus-related cancers respond quite well to radiotherapy.

And so it is true on page 80 I gave an answer that if I had more time to think or if I could redo it, I would put it a little bit differently. But as we went on with questioning, clearly there are times when I do give an etiology for a particular patient's cancer.

Q. Well, human papillomavirus is not one of the claimed cancers that's at issue in this litigation, is it, Doctor?
A. Well, I was speaking of an example; I was not speaking directly to this litigation.
Q. And you submitted an errata to your deposition, is that right, where you had a chance to read your deposition and make any corrections?
A. I don't recall submitting any errata.
Q. Well, nonetheless, your chosen choice of words were -- were that the etiology never goes into a report.

And in some other examples, you were asked about, well, have you ever used the words "pharmaceutical-induced cancer" in your pathology reports? And the answer is no. Correct?
A. I would be -- so pharmaceutical-related injury has gone into my reports dozens or hundreds of times, but pharmaceutical-related cancer, no.
Q. That would not be something you would put in your report -- in a pathology report you generated. Correct?
A. Well, the state of knowledge previously, there -- there aren't many examples that I can think of of pharmaceutical-related cancer prior to this issue coming to light. So this is not something that I would have put in a report previously. I'm not sure that I would agree that I would never put it in a report going forward.
Q. All right. Well, this issue came to light, and I believe

you were retained back in 2018. Correct?
A. It seems a little early to me, but I don't totally recall.
Q. So you don't know when the issue of nitrosamines in valsartan was first discovered and reported by the FDA?
A. Oh. That is 2018. I was talking about when I was retained I don't recall.
Q. So since 2018, you've never put in a pathology report you've generated the words "pharmaceutical-induced cancer" or "valsartan-induced cancer." Correct?
A. Correct.
Q. And as a matter of fact, a patient's history in taking NDMA is not something that would normally be provided to you, is it?
A. On the scale of carcinogenesis, this is still a very new issue, so, you know, before 2018, there would have been no real reason, at least with respect to medications, to include that sort of history on a pathologic requisition. What happens in the future, I don't know.
Q. Okay. Well, Dr. Lagana, if you could turn with me to page 83 of your deposition, line 1.
A. Okay.
Q. You were asked: And sitting here today, you can't think of any time when you thought that something was NDMA or NDEA induced. You can't come up in your mind of any instance where

you thought that was the cause or genesis.

And your answer was: I think a patient's exposure history to NDMA is not something that would normally be provided to me. It's not something that would typically enter my thinking.

Were those your words, Doctor?

A. Sorry, what page and what line were you talking about?

Q. Page 83, line 1, sir.

A. 83. Okay. Sorry, I was on 81.

Q. No problem.

A. Yep, that's what I said.

Q. All right. And before this valsartan litigation and your meeting with Mr. Slater in the fall of 2020, you had never done any research outside of the litigation on NDMA or NDEA. True?

A. True.

Q. And prior to this litigation, the question of whether ingestion of NDMA or NDEA as an impurity in valsartan and whether that can cause cancer in humans had never even come up in your practice. Correct?

A. I wouldn't have expected it to, but no.

Q. But as a scientist or a clinician or an MD, you had never looked at this issue before. Correct?

A. Well, I wouldn't say that. I mean, it depends how specific you want to define this issue as. Certainly I had

some background knowledge of nitrosamines and what they are thought to do before I entered into this litigation. I did go to medical school, and I performed a residency and fellowship.

Q. I understand. But the specific question I'm asking you is, as a scientist or a medical doctor, prior to being retained, you had never looked at the issue of whether nitrosamines in valsartan causes cancer. That's a true statement. Right?

A. Yes. When Mr. Slater gave me this question, I approached it with an open mind. I didn't have a preconceived sense that the amount of nitrosamine in valsartan would or would not cause cancer. I went through the literature, and I performed a literature review the same way I would if I was writing a review article of which I've written several.

Q. Right. And we'll get to that in a moment.

But my question to you is that you've been retained by Mr. Slater before, in the Benicar litigation. Right?

A. Correct.

Q. And in the Benicar litigation, the diagnostic approach you took there was standardized, and it was the approach utilized in your clinical practice. Right?

A. I am both a clinician and a researcher. Research is my second largest responsibility at work. And so I -- there are clinical methods that I use. If Mr. Slater were to want to ask me about a particular patient in this matter, I would look

at the slides and the history in the same way I described in Benicar when multiple cases were presented to me.

In Benicar, I also looked at the question of general causation. And in that sense, I reviewed the literature in the same way I do here, which is to take an open -- open mind, look through the literature, weigh the evidence, and use my judgment to draw a conclusion.

Q. Well, in Benicar, you started with a review of clinical information for the patients and the slides for those plaintiffs. Correct?

A. I don't remember which I did first.

Q. Okay. Take a look at page 104 of your deposition, please, sir.

A. Okay.

Q. Down on line 16, you were asked: And then when we get into Benicar in 2016 in your report, or 2017, you said, quote, the diagnostic approach I take to such cases is standardized and is the approach utilized in my clinical practice in connection with the studies of authors in the peer-reviewed medical literature and presentations given at major professional meetings.

I start with the review of very basic clinical information, generally limited to the presenting symptoms, for example, diarrhea, and then begin my slide review. Right?

And your answer was: Remains true.

Next question: And that's how you do your clinical work also. Correct?

And you said yes.

Is that testimony still accurate, sir?

A. 100 percent, but we're conflating clinical work and research work.

Q. Right. I understand. But my point is that the standardized approach you described as what you used in Benicar is not the same approach you used in valsartan where you didn't have clinical patient information, data and slides. Correct?

A. I'll rephrase what I said before, which is -- more accurately is you're conflating clinical work and research.

If I was asked to review a particular patient's case and determine whether I believed that individual person's cancer was caused in part or in total by valsartan, I would follow the exact process that I described in this snippet that you just read. That's how I approach a clinical case.

As a researcher, I have written many review articles in which I did not personally review any cases. I looked at the literature. And those have been peer-reviewed, and some of them have been widely cited. So in my second role as a physician researcher, the researcher part, that does not play out in the same fashion as looking at a particular patient's pathologic material does.

Q. I'm just simply asking you about your methodology in Benicar as an expert witness versus your methodology in the valsartan litigation as an expert witness.

Do you understand?

A. The difference is -- there's a difference between general causation and specific caution. And the things that you're talking -- the examples that you're reading are the way I would approach the question of specific causation, not the way I would necessarily approach the question of general causation.

Q. And in this case, though, you're not being asked to give a specific causation opinion. True?

A. Thus far I have not been asked to opine about any specific patient.

Q. Now, in your practice, in your research engagements, you've never researched to publish an epidemiology review answering the question of general causation. Correct?

A. Well, I've written several review articles with subcategories on epidemiology, specific subheadings of epidemiology as well as causation. So I think that that is an incorrect -- it's a very, very precise wording that you used there. I don't quite know exactly how to answer it.

But the -- but if the general question is, have you ever done research studies dealing with epidemiology and causation, the answer to that is absolutely. And they've been published

in the peer-reviewed medical literature.
Q. But you've never published an article that answers the question, based on a literature review, does exposure X cause cancer in the general population. Correct?
A. I'd need to take a few minutes to look through my bibliography.
Q. Well, I'm sure plaintiffs' counsel can address that with you on redirect if needed.
Let me change gears for just a moment.
In looking at your certification, you represent that you took into account the various categories of medical and scientific literature. Correct?
A. Correct.
Q. But your discussion of valsartan in your report was focused almost exclusively on NDMA. True?
A. NDMA is by far the most prevalent nitrosamine in humans, and so, you know, the majority of the research that's available to review does deal with NDMA. But there are certainly examples in my report where I speak to the potent carcinogenicity of NDEA, such as -- just give me one second -- the Thresher paper and the Zheng paper on pancreatic adenocarcinoma.
Q. And those --
A. And also --
Q. Go ahead.

A. That's okay. I'm done.
Q. Right. And so it's true that NDMA is by far the most commonly studied nitrosamine of the two. You agree with that. Right?
A. I do.
Q. Now, despite there being significantly more literature addressing NDMA than NDEA, you felt it was appropriate to extrapolate NDMA literature in rendering your NDEA opinions. Correct?
A. I wouldn't put it in such a black and white phraseology. I did review original medical literature related specifically to NDEA. I gave two examples a moment ago. I don't know that those are the only examples, but they're the ones that come to mind. And furthermore, I went with the -- I did also follow the guidance afforded by WHO who has said that the two should be looked at equivalently.

Further, I read what FDA said about the issue. And actually, FDA set the acceptable maximum limit of NDEA quite a bit lower than NDMA, implying that they too consider it more dangerous even than NDMA.

So given imperfect evidence, not as robust as NDMA, as you said, I addressed it in as scientific a method as I could -- as I could. And I think I did do that fairly.
Q. But the only two peer-reviewed, published articles you can cite to that address NDEA are Thresher and Zheng. Right?

A. No, I don't agree with that at all. Those are the two that are on the top of my head. I mean, I did not study as if I was going to be given an exam on this. I'm happy to go through the report again and look at the details of everything. The fact that only two of them come to my mind is really immaterial. That's a question of my memory, not a question of what I looked at.

Q. Well, certainly you expected you would be asked these questions today. Correct?

MR. SLATER: Objection.

BY MS. LOCKARD:

Q. About --

MR. SLATER: I'm sorry, Your Honor, again, I'm very, very, very hesitant to object, but the word "NDEA" doesn't even appear in this certification. Again, I'm being very, very restrained, but I would object at this point and ask to get back on course.

MS. LOCKARD: Well, Your Honor --

THE COURT: Counsel, where are we going with this? He doesn't discuss NDEA in this certification.

MS. LOCKARD: Well, correct, but he does say in his certification in paragraph 3 that I evaluated and took into account various categories of medical and scientific literature and that that formed the basis for his methodology.

My point is that the various categories of medical

and scientific literature did not include NDEA literature.

THE COURT: Well, but paragraph 3 is in response to what the defense raised about null hypothesis. And he's trying to explain where he began. It has nothing to do with NDEA. So let's move on, please.

BY MS. LOCKARD:

Q. Okay. Dr. Lagana, the question you were asked to answer in this case is whether ingestion of NDMA and NDEA as a contaminant or impurity of valsartan is a cause of cancer in humans. True?

A. Well, I would say the question was -- basically I agree with you. But just to make the wording a little bit more refined, I would say the question I was asked to answer was, is the NDMA and NDEA that contaminated valsartan pills probably or a probable carcinogen to the humans who ingested those pills or not. And I did approach that question from a neural standpoint, weighing the evidence, positive and negative studies and equivocal studies, all of which I considered, and I reached a judgment, which is in my report.

Q. Well, Dr. Lagana, if you could turn to your deposition, page 21, line 17. Let me know when you're there.

A. Uh-huh.

Q. You were asked, you understand -- and again, in this report you start with a sentence that says: This report sets forth my opinions with regard to the question of whether

ingestion of NDMA and NDEA as a contaminant or impurity of valsartan can cause cancer in humans. Can cause cancer in humans.

Did I read that correctly?

A. Yes. And I believe that's what I just said.

Q. Well, the question, you would agree, of whether NDMA or NDEA can cause cancer in humans is a different one from whether it is a probable human carcinogen. Right?

A. I --

Q. I'll move on, Dr. Lagana.

You've heard and read that the scientific method should start with a null hypothesis, which is a hypothesis that there is no association of causation unless it's proven otherwise. Right? You've heard that.

A. Yeah. The null hypothesis is the statistical starting point of any scientific experiment and it's why we set a p-value for significance at .05. So if I do an experiment and I get a positive result and the p-value is .51, that's really -- or sorry, .49, that's really saying that it's more likely than not that my experiment is true. But it's only 2 percent more likely, so it's -- so because we have to start with the null hypothesis in statistics, we as a medical and scientific community have set the typical acceptable p-value as .05.

So meaning that, you know, there has to be less than a

5 percent chance that an association is -- is a false -- a false signal for us to take the results as positive.

Q. But you don't believe you were required to start from the null hypothesis because you didn't perform a statistical analysis. Right?

A. Well, we can colloquially talk about null hypothesis in that you should keep an open mind. And I did keep an open mind. I approached this question without a preconceived concept that NDMA or NDEA in valsartan pills were going to cause cancer in humans. I approached it with a open mind and a neutral starting point, and I read the literature and reached my judgment.

Q. Well, in your certification you attempt to explain your commentary on the report about your assumptions going into the case by saying that you were simply discussing the concept of a differential diagnosis. Correct?

A. I'm sorry, my assumptions about -- I'm not sure I understand exactly what you're asking me.

Q. Well, in your report, and what we asked you about on cross-examination in your deposition and what we raised in the briefing, is a comment that you made in your report on page 11 and 12 that states: In any patient who develops cancer and is known to have a significant exposure to a probable human carcinogen, it should be assumed that the carcinogenic exposure increased the risk or contributed to the cancer.

That was from your report. Correct?

MR. SLATER: Objection. It's not an accurate reading of what the report says. It's an inaccurate paraphrase.

BY MS. LOCKARD:

Q. Okay. Let's take out the report and turn to page 11 and 12, Dr. Lagana.

A. Sure.

Can I respond now or wait --

Q. Let me ask my question.

A. Sure.

Q. So if you put down -- about halfway down the page there's a bold heading. And the heading says: Does NDMA likely cause cancer in humans at the levels in the contaminated valsartan? Correct?

A. Yes.

Q. And is that -- that's the header you drafted yourself. Right?

A. Correct.

Q. You authored it?

A. Yes.

Q. And that is the general causation question, is it not, does NDMA likely cause cancer in humans at the levels in the contaminated valsartan?

A. Absolutely.

Q. That's not a specific causation inquiry, is it?

A. That, no. That statement does not refer to specific causation. It's a general causation question.
Q. So if you follow along with me, third sentence after this general causation heading --
A. Uh-huh.
Q. -- you state: Therefore, for any patient who develops cancer and is known to have a significant exposure to a probable human carcinogen (the levels documented above constitute a significant exposure in my opinion), it should be assumed that the carcinogen -- or excuse me, carcinogenic exposure at least increased the risk or contributed to the subsequent cancer, unless there is a convincing body of evidence to suggest that the carcinogenic insult is null with respect to the specific cancer in question.

So first of all, did I read it correctly that time?
A. Definitely.
Q. Okay. Embedded in this sentence is the assumption that you're representing should be made that a carcinogenic exposure at least increased the risks or contributes to the cancer unless there's convincing evidence otherwise. That's the essence of your statement. Correct?
A. Well, again, we're conflating the idea of a particular patient with the idea of general causation. So as it states very clearly -- I'm not done.

As it states very clearly in this sentence, for any

patient who develops cancer. And as it goes on to say, it should be assumed that the carcinogenic exposure at least increased the risk or. So a carcinogen is something that increases the risk of cancer. It's basically definitional.

And so what I'm talking about in this sentence is how I would approach a particular patient if the general causation question had already been firmly established. For example, if I see a patient who has been smoking cigarettes for 60 years and develops a lung cancer, it would be wildly inappropriate to say, hmm, I wonder -- let me take a few years to study -- you know, to start researching whether it's possible that cigarettes can cause lung cancer.

The research is established. The association and causative nature of the relationship is clear. And as a physician treating a specific patient, not answering a general question, I would apply -- I would use the applied medical literature to answer the question.

Q. Well, I understand the explanation that you've given in the certification, Dr. Lagana, but the fact is, you're not being asked in this case to make a specific causation determination. Correct?

A. I have not thus far been asked to make a specific causation -- to opine about the specific causation in any specific patient.

So this -- this sentence that we're talking about here

really doesn't even relate to the question of general causation. It's quite clear because it does say for a patient in it.

Q. Well, and that's my point as well. If these statements don't relate to the question at hand, it's not helpful to the exercise today, is it, Dr. Lagana?

A. Give me a moment to think about how I'd like to answer that, please.

Well, look, I'm not a professional witness. I'm a doctor. I perform research. Perhaps I put more thinking or I explain more of my thinking in more depth than was needed to in this report, and it has certainly given people who are motivated to misunderstand me tremendous opportunity to misrepresent what I said, even though the specific words are in the sentence, including for any patient.

Q. And I certainly don't intend to misrepresent you, Doctor, but these are your words. You wrote this report. Correct?

A. And the words are true and correct. You keep misunderstanding them or misstating their meaning, when I believe we've said several times at this point that it relates to dealing with a specific patient if the science is already settled.

If the defense believes that the science is totally settled, that the amounts of NDMA in these pills are probable human carcinogen, then, I mean, we could just -- you should

settle the case now.

Q. Well, you understand, don't you, that the science isn't settled with respect to general causation, unlike your cancer-smoking analogy. Right?

A. Well, I think the science is less mature than cigarette smoking and cancer, but I have looked through quite a bit of literature, all of which is cited or most of which is cited in my report. And I have given weight to the various forms of evidence, and I have come to the conclusion, the conclusions that are stated in my report.

So I -- to me, it is certainly more likely than not that the amounts of NDMA in contaminated valsartan are carcinogenic in humans.

Q. Exposure to cigarette smoke is a known carcinogen. Correct?

A. Yes.

Q. It's a group 1 carcinogen as determined by IARC. Right?

A. Yes.

Q. You're aware, that's not the case with NDMA or NDEA. It's not a known carcinogen according to IARC. Correct?

A. It's a probable human carcinogen according to IARC.

Q. Now, I understand that -- this language that you have put under -- in your report under the general causation heading, you now say in your certification that that really goes to a differential diagnosis.

But no --
A. It was --
Q. -- nowhere in your report do you even talk about differential diagnosis. The words "differential diagnosis" don't even appear in your report, do they?
A. I'd have to have it virtual -- on my computer and control-F it to know for sure, but that statement is an ex -- it starts -- it's an introductory statement to how a doctor approaches a particular patient.

And then I get into the, you know, dozens of studies regarding NDMA and NDEA in human cancer. And those are the studies that form the basis of my general causation opinion.

These sentences that have been plucked out and misrepresented in my opinion are background sentences about how I would approach a specific patient with cancer, not how I would answer a general causation question.
Q. Right. And that's not surprising given that 75 percent of your time is dealing with specific patients, correct, as opposed to answering a general causation question?
A. Yeah. Earlier you mentioned that my -- you kind of tried to get into my job description. And yes, clinical medicine, anatomic pathology, is 75 percent of my life.

But the next largest area is research. And also, I don't want to draw some phony distinction between clinical practice and general causation of disease. Pathology is the study of

disease. That absolutely includes the causation of disease. So thinking about, reading about and talking about causation of disease is part and parcel of what I do almost every day.

I'm a teacher as well. That time when I'm doing clinical work, I'm also often about half that time, I have a trainee with me, and I'm explaining to that trainee causes, manifestations, everything else that's part and parcel of disease, which is absolutely a pathologist's business.

Q. Doctor, did you apply the null hypothesis in this case, yes or no?

A. I didn't do a statistical analysis, so I didn't use null or not null hypothesis. But colloquially, I did approach it with an open and neutral position, and I looked at the literature to convince me one way or the other.

Q. Did you adhere to the scientific method?

A. Yes, to the extent that you can when you're not performing experiments. I mean, the scientific method is hypothesis-driven -- generally speaking is hypothesis-driven experimental work. I didn't do any experiments. I didn't have a hypothesis.

As I've mentioned before, I have written several review articles in the peer-reviewed medical literature. And that entails exactly what I did here, which is to pick a topic. In this case I was provided a topic. And look at what I considered to be the relevant original research and use my

judgment to form an opinion based on the weight of the evidence. That's what I did.

Q. So just so I understand, so you did not start with a hypothesis when you approached this case?

A. That's true.

Q. And your position is that's not required because you didn't do any original clinical research, and you didn't do any statistical work. Right?

A. Correct. I started with a neutral mindset. I had no particular opinion one way or the other.

Q. In your description and explanation of your methodology and process for reaching a conclusion, you likened this case to a scenario of whether jumping out of a ninth floor building causes harm.

Do you remember that discussion?

A. I think you're misrepresenting the discussion. I did use that analogy, but I don't believe it was in the context of whether -- of any specific case. I think it was a general statement.

Q. Well, your position was that in some situations, you can just use a little bit of common sense rather than the null hypothesis. Right?

A. In some situations, yes. In a general sense, yes. I never said that that's what I did here or that that statement even has anything to do with this litigation.

Q. Right. Obviously, this is not one of those situations where the conclusion relies on common sense. Right?
A. Well, any conclusion worth making usually requires a little bit of common sense, but for the most part, I would agree with you, that to have a conclusion here requires a careful analysis of the literature, the medical and scientific literature, and requires one to -- at some level, I mean, one does have to make a judgment. There are a number of papers. In my opinion, most of them clearly go in a certain direction, and that's using the weight of evidence. I reached my conclusion. But there does -- there is an element of human judgment in this matter.
Q. Right. But if a conclusion can be reached based on common sense, then we don't need experts like yourself to come in and explain it to a jury who has already possessed their own common sense. Right? That's my point.
A. Sure. Of course, there's no -- common sense does not answer this question by itself, no.
Q. So you don't agree that the Bradford Hill methodology itself requires that -- that requires a null hypothesis in the beginning of the review prior to applying the nine viewpoints?
A. Well, Bradford Hill is a guideline. It's a way to evaluate the epidemiologic and other forms of literature, but originally epidemiologic.
I think -- I think it requires -- to apply it fairly

requires starting from a neutral position, which is what I did here. Whether you want to call that the null hypothesis, it's sort of misusing the term. So I do think if you start with a preconceived answer and just cherry-pick stuff to support your preconceived answer, that would not be a proper application of any methodology, including Bradford Hill's.

Q. So --

A. That's not what I did here in any sense.

Q. So just to be clear, you do not agree that the Bradford Hill methodology requires a starting point with a null hypothesis. Correct? That's your testimony?

A. My testimony is that in spirit, I think that it basically does, but it's using an overly technical term in my opinion that's incorrectly used in that context.

Q. Dr. Lagana, your certification explains that you took into account the various categories of medical and scientific literature and evidence discussed in your report.

And those -- the categories that you're referring to, those are the citations that are listed at the end of your paper. Correct?

A. At the end of my initial report?

Q. Yes.

A. Yes, yes.

Q. Now, your references cited did not include and 2021 article entitled "Permitted daily exposure limits for

noteworthy N-nitrosamines" by Dr. George Johnson, did it?
A. What is the date of publication on that article?
Q. It is April 2021.
A. April 2021.
Do you have the date of my...
When was my report filed? July 2021.
What is the citation again?
Q. The title of the article is "Permitted daily exposure limits for the N-nitrosamines" that was written by Dr. George Johnson. It's not on your citation list. Correct?
A. Allow me to review it. I don't recall.
No, I don't believe that I did rely on that study.
Q. And so you don't recall coming across Dr. Johnson's paper when you did your literature review and research?
A. I don't recall, no.
Q. And so Dr. Johnson's paper did not factor into your weight of the evidence analysis. Correct?
A. Nope, not if I didn't see it.
Q. And you were asked about this article in your deposition.
Have you not gone back to look at this article since you were deposed?
A. I don't remember the questioning, and I did not go look for the article.
Q. Well, I'll be glad to direct you to page 25 of your deposition, if necessary, to refresh your recollection --

A. Okay.
Q. -- line 25.
And you were asked: Do you know Dr. Johnson, a toxicologist, who came out with a recent article on NDMA and NDEA?
And your answer was no.
Have you ever heard -- excuse me. You never heard of him?
Not that I recall.
Did you read his article?
You said: We'd have to check the list.
And the question to you was: Sitting here right now, do you have any recollection of reading Dr. Johnson's recent article that came out in 2021?
And your answer was: I might recall the article. I don't recall the name. I'd have to see what article we're talking about.
Do you see that testimony?
A. Yes, yes.
Q. Okay.
A. I'd never read the article before or since, or I have no recollection of having seen the article before or since.
Q. So did you not think that a recent 2021 article on "Permitted daily exposure limits for noteworthy N-nitrosamines found in valsartan" would be important to your opinions in

this case?
A. Well, certainly it'd be -- if I were to be called to trial, it would be extremely important for me to fill in all the -- to review all the literature that's been published from the time when I drafted my report until the time that I was going to speak to a jury. I don't think that I need to be constantly monitoring it. I think it's -- I have not produced a document with new opinions, so I have not -- I don't think that it's necessary to talk about -- about my methods. Looking at a new study is a new study. And I'd be happy to deal with it and present it -- you know, present my opinions to a jury on it should that become relevant. But that has nothing to do with my methods that I took into -- that I used to produce this report.
Q. Well, you understand that you're testifying here today under oath in an MDL in federal court before a federal judge to defend your methodology. And you didn't think that it was important to go back and review the literature you'd relied on?
A. I did review some of the literature I relied on. I believe I just told you that the study that you're highlighting is not one of the studies I relied on.
Q. Now, keeping in mind that there is a dearth of literature published specifically on NDEA, wouldn't you want to see Dr. Johnson's paper if it addresses NDEA?

A. Well, I have no knowledge of the paper, so it's hard for me to speak to it, but I'd certainly -- if I were to be asked, again, to opine about my general causation opinions, I would review any literature that had been published in the time between my production of the -- of my report and me delivering my opinions again.

Q. Well, you were made familiar with the paper when you were asked about it in your deposition last year. Correct?

A. It was mentioned to me. I was questioned for nine hours. I'm sorry, I don't, you know, go home and start poring through PubMed.

Q. Now, shifting gears for a moment, you -- in your literature citations, you also cite to the WHO document. Correct? That's another document you relied upon?

A. Yeah. There were several. I believe there was more than one WHO citation, but, yes, the WHO's comments did inform my thinking, along with the rest of the medical and scientific literature.

Q. Well, and one of the bases for the WHO's conclusion about carcinogenicity of nitrosamines according to your report was the direct interaction with DNA consistent with tumor formation.

Do you recall that from the WHO?

A. If you could just point out the part of my report that you're referencing, I'd like to look it over for myself.

Q. Sure. It's page 12 and note 18, right in the middle of the page.
A. Uh-huh.
Q. So in your report, you're talking about the World Health Organization issuing a summary analysis. Right?
A. Correct.
Q. And you go on to talk about what the authors observed, and you quote from the WHO: "Putative pathways for the metabolism of" DNMA -- excuse me -- "NDMA are similar in rodents and humans, and indeed the formation of the 06-methylguanine have been detected in human tissues exposed to NDMA." They concluded, "Therefore, owing to the considerable evidence of carcinogenicity in NDMA in laboratory species, and evidence of direct interaction with DNA consistent with tumor formation..."
That's the reference I'm directing you to. Do you see that?
A. Yes.
Q. So my question to you is, did you in your literature review take into account categories of medical and scientific literature addressing the impact of DNA --
A. Sorry, there was a ding there.
Addressing what?
Q. I'll repeat it.
My question to you is, when you did your literature

review, did you take into account categories of medical and scientific literature addressing the impact of DNA repair?

A. Absolutely. Yes. I have a rather lengthy section about Lynch syndrome, which is a congenital deficiency of DNA repair. So, yes, I did -- I did indeed think of DNA repair.

Q. Other than your reference to Lynch syndrome in your discussion of the Danish study that you cite in your report -- other than discussion of Lynch syndrome, there's nowhere else in your report that you considered or discussed the DNA repair. Correct?

A. Certainly not true. I considered it. It's pathobiology of cancer. You can -- I considered it throughout the drafting of the entirety of the report. DNA can be injured by various substances, including nitrosamines. And oftentimes that insults or that injury is repaired, and sometimes it's not. And when it's not, then you get a tumor. So that's just pathobiology. And I did discuss it, that pathobiology, in detail in the section about Lynch syndrome.

So to say, you know, I didn't think about it and didn't write about it is totally inaccurate. I did think about it and included it in my report.

Q. Well, my question is not did you think about it, but did you actually look into the research on DNA repair?

A. Well, your question was did I consider it. You used the words "did I consider it?" And I absolutely considered it.

As far as did I look into the research on DNA repair, to an extent. And I quoted -- I cited it in the context of Lynch syndrome. But also, it's background knowledge that I have that I know well. It's part of my training.

Q. Okay. So in rendering your opinion, you didn't think that it was necessary to do any literature review with respect to DNA repair mechanisms then. Is that fair? You just relied on your background and training?

A. I believe I said pretty clearly at least twice that I did cite literature related to this in the context of Lynch syndrome.

Q. Outside of Lynch syndrome, did you do any research into DNA repair mechanisms?

A. I mean, as I sit here today, except for the example in which I did do it, I don't remember a second example.

Q. You agree that dose and length of exposure are reasonable things to consider when testing the hypothesis. Correct?

MR. SLATER: Your Honor, again, I would object at this point. I believe that counsel's gone so far beyond the certification that at this point I would ask that counsel be limited to the certification.

THE COURT: Sustained.

Let's focus, please, on the certification.

BY MS. LOCKARD:

Q. Well, your various categories of medical and scientific

literature that you took into account, as mentioned in paragraph 5 of your certification, those categories did not take into account specific literature regarding a dose-response curve. Correct?

A. Completely incorrect.

Q. You did not look at specific literature addressing a dose-response curve by each of the cancers alleged in this case, did you?

THE COURT: Excuse me. Let me interrupt.

Counsel, paragraph 5 of the certification is a continuation of his discussion of null hypothesis. It doesn't open the door to all the questions you asked him at his deposition and all the grounds that you submitted in your motion. Let's move on to what's in the certification, please.

MS. LOCKARD: Okay. I understand, Your Honor. I hear you.

BY MS. LOCKARD:

Q. In paragraph 6 of your certification, Dr. Lagana, you provide the example that you briefly referenced earlier regarding a patient with cancer who is a lifetime cigarette smoker. In that case, one would have a high index of suspicion and place cigarette smoking high on the differential diagnosis.

Do you see that in your certification?

A. I do.

Q. When making such an assessment to place cigarette smoking on the differential, wouldn't it be important to you to assess the dose and duration of the smoking?
A. Yes. Well, I think I said -- hold on one second.
I believe I said a lifetime cigarette smoker in my certification. So yes, that would include, obviously, considerations of dose and duration.
Q. So the statement in your report recognizes that dose and duration are important when you're deriving a differential diagnosis for a particular patient as to the cause of their cancer. Correct?
A. I don't think it's controversial to say that more cigarette smoking throughout one's lifetime is more risk to you than less. That's well established. And I do. I have no argument with the idea that dose and duration are important when looking at any carcinogen.
Q. You would agree that that's true for any carcinogen, correct, that more of the carcinogen is bad, less is less bad. Correct?
A. That's a very general way of putting it. I think that, you know, there are -- for some carcinogens there are threshold levels. I wouldn't want to -- generally, I agree with what you just said.
Q. Wouldn't it also be important to consider the type of cancer when presented with a cancer patient with a history of

smoking, to determine etiology?

A. Absolutely. I think I said lung cancer in this example that I gave, or at least I hope I did. Yes. Cigarettes are well known to cause cancers of the lung, they cause cancer of the bladder, they cause cancer of the head and neck. There are some cancers that they specifically have been shown not to cause, such as mesothelioma, for example.

So yes, the specific cancers are relevant when considering the impact of a carcinogen.

Q. Well, in fact in your statement in your certification you don't specify lung cancer.

A. Okay. I should have.

Q. Okay. And just like in your report and conclusions, you discuss the risk of cancer generally, but you don't specify individualized risks for each of the cancers that are alleged in the suit, do you?

A. I'm not sure I totally understand the question. I dealt specifically with whatever cancers were specifically in the literature, such as gastric cancer, colorectal cancer, brain tumors, lung cancer, liver cancer, pancreatic cancer. These are the ones that -- bladder cancer, kidney cancer, ureter cancer. These are the ones that come to mind as having had specific literature references -- oh, esophageal cancer of course.

Q. But you didn't do a Bradford Hill analysis with respect

to each of these individual cancer types. Right?
A. Each of those cancer types went into my overall Bradford Hill analysis.
Q. Right. But your overall analysis was applying the nine viewpoints to the issue of cancer in general, not specific cancers. In other words, you didn't take a body of literature that related to liver cancer and apply the nine viewpoints from Bradford Hill to that body. Right?
A. Well, one of the important mechanistic pieces of this was entry into the bloodstream. And I did deal with that directly in my report. When the carcinogen does get into the bloodstream, it becomes quite plausible that it can cause cancer in generally any organ that receives blood.
A counter-example, for instance, would be asbestos. Asbestos is a terrible carcinogen. It causes cancers, well established to cause cancers of the lung and pleura, but it doesn't get into the blood. So no one's had, like, I don't know, brain cancer because of asbestos. So --
Q. And the answer to my question, respectfully, Doctor, was no, you did not do an independent Bradford Hill analysis for each of the cancer types. Right?
A. Well, I considered the viewpoints and I considered the weight of the evidence. I did not do a formalized Bradford Hill recitation for every type of cancer that is likely to be caused by contaminated valsartan.

Q. But you would agree there was some inconsistency in the literature when you look at these individual cancer types in terms of the findings from the reports. Right?

MR. SLATER: Your Honor, I would place the same objection.

MS. LOCKARD: I'm wrapping up, Judge.

THE COURT: Let's get it done, please. Let's get focus back on the certification, please. Thank you.

BY MS. LOCKARD:

Q. Dr. Lagana, in terms of your literature review and your Bradford Hill analysis which you have described, you didn't seek to do an individual analysis from the literature or the various categories of literature mentioned in paragraph 5. You didn't do that, did you?

A. I did apply a weight of evidence approach to the specific cancers where I felt -- where I felt it was appropriate.

Q. And then in your conclusion, you lumped your conclusions in your report into one statement regarding the risk of cancer, the potential causation of cancer in general. Correct?

A. What exactly are you referring to?

Q. Well, you didn't seek to determine if there were different dose curves for each of the cancers. You didn't provide any analysis of different latency periods for each of the cancers. Correct?

A. I discussed dose curves when they were available. I discussed latency in the few examples in which it was available. Whether I applied -- discussed those concepts in detail in every type of cancer, I don't recall. But certainly if I was looking at an individual patient, those would be things that I would take into account.

Q. Correct. But looking at individual types of cancers, you didn't do that in your report?

A. That's not true. I mean, there are plenty of references to dose within the report related to specific cancers.

Q. But you didn't do a Bradford Hill analysis taking into account the literature on a cancer-by-cancer basis. Right?

A. I worked with the guidelines in mind. And I took a weight of evidence approach with respect to each individual cancer.

Q. So your opinion in this case is the same regarding colorectal, gastric, bladder, blood, pancreatic, esophageal, prostate, lung or kidney, in terms of the relative risk presented?

A. No. I didn't say that.

Q. Well, where in your -- where in your expert report do you make an effort to assess individualized cancer risks? It's not in there, is it?

A. It's certainly in there. Absolutely. I reviewed the literature, and in places -- and with respect to specific

cancers where there are ranges of increased risk, absolutely. That's all over my report.

Q. Well, you discussed the literature in your report that was part of your various categories of medical and scientific literature review. And where the literature discussed a particular cancer, you included some of that language. Right?

A. Yeah. Where the literature gave a relative risk, and particularly when it equated it to a particular dose, I absolutely included that discussion in my -- in my report as much as I could.

Q. Well, in your final conclusion in the case, however, after looking at that body of literature that did provide information about individualized relative risks of various cancer, instead of putting that information into your conclusion, your overall conclusion was all have an increased risk of cancer as a result, and as a general matter, without reference to individual predispositions or concurrent risk factors, further increasing the risk on a case-by-case basis, the larger the contamination and/or dose and the longer used, the higher the increased risk of cancer. Cancer generally.

Correct? That was your conclusion in your report?

A. Well, the conclusion at the end of the report doesn't negate any other conclusions that were drawn throughout the body of the report. It's one report.

And so if I looked at -- if we look at -- if we turn to

the page on colorectal cancer -- let me find that.

On page 13, for example, that's looking at a study of -- a dietary study with respect to colon cancer. And they found that there was a 46 percent increased risk of rectal cancer compared to -- in high consumers of NDMA compared to low consumers. And they actually also were able to put together a dose for that, which was 126 nanograms per day.

So in this example, we had both an odds radio or an -- a specific increased risk and a dose.

And as I go through the papers, you know, the next paragraph also shows what the strength of the association was, how much elevation and risk was there.

So, you know, these are -- these paragraphs, they summarize the increased risk with respect to colorectal cancer.

Then if you look at page 14, I get into stomach cancer and do the same -- the same thing.

So the fact that on the conclusion page paragraph I don't rehash everything that has been in the report prior to it is in no way a disavowal or a negation of everything that went into the remainder of the report.

Q. Well, just taking NDEA for an example, you identified Thresher and Zheng as literature supporting your opinion that NDEA in the amounts in the valsartan caused cancer.

How do those two articles, the only finding of a

statistical significance at all was with respect to pancreatic cancer from NDEA. Correct?

MR. SLATER: Your Honor, once again, I'll object. I think we actually addressed NDEA and Your Honor asked counsel to move on. I feel like we're going back to an area that was already moved on from.

MS. LOCKARD: Your Honor, I appreciate that. Those are all the questions I have at this time.

THE COURT: Thank you.

Mr. Slater, did you want to ask any questions?

MR. SLATER: I have no questions, Your Honor.

THE COURT: All right. Why don't we take a ten-minute break and we'll get set up for the next one. Okay?

MR. SLATER: Thank you very much.

MS. LOCKARD: Thank you.

THE COURT: Thank you, everybody.

(Recess at 10:57 a.m. until 11:08 a.m.)

THE COURT: Mr. Nigh, you ready? Mr. Trischler, you ready?

MR. NIGH: Yes, Your Honor.

MR. TRISCHLER: Yes, Your Honor.

THE COURT: Let's get started. The witness is here, I see.

THE WITNESS: Yes, Your Honor.

THE COURT: Dr. Panigrahy, how are you?

THE WITNESS: Good, good. Thank you.

THE COURT: Raise your hand. I'm going to put you under oath.

DIPAK PANIGRAHY, MD, PLAINTIFFS' WITNESS, after having affirmed, was examined and testified as follows:

THE COURT: Would you state your full name, please, sir.

THE WITNESS: Dipak Panigrahy.

THE COURT: Thank you.

Mr. Trischler, you may begin, sir.

MR. TRISCHLER: Thank you, Your Honor.

Before I do, in the event that there are certain exhibits that are made part of the record, does the Court have a preference for purposes of this hearing as to how we identify Panigrahy-A, B, C, or whatever method the Court prefers?

THE COURT: Have you previously identified them at depositions and do you want to keep the same system? It's up to you.

MR. TRISCHLER: Some we may have, but I can't say for certain. That's why -- whatever the Court's preference is.

THE COURT: Well, probably Panigrahy-1 through whatever would work. Thank you, sir.

MR. TRISCHLER: All right. Then we'll proceed in that fashion. Thank you, Your Honor.

May I begin?

THE COURT: Please do.

MR. TRISCHLER: Thank you.

DIRECT EXAMINATION

BY MR. TRISCHLER:

Q. Dr. Panigrahy, good morning.

A. Good morning, sir.

Q. In your supplemental declaration that is dated February 24, 2022, you cite three articles that were published by Gombar that deal with the pharmacokinetics of NDMA in certain animal species. Is that true?

A. Yes.

Q. And for the record, a paper that's entitled "Pharmacokinetics of NDMA in beagles," a 1987 paper; is that right?

A. Yes.

Q. And I will have that paper marked as Panigrahy-1. All right?

And then you have a second paper that you referenced entitled "Pharmacokinetics of NDMA in swine," a 1988 paper; is that correct?

A. Correct.

Q. And we'll mark that as Panigrahy Exhibit 2. Okay?

A. Thank you.

Q. And then there's a third paper that you cite to entitled

"Interspecies scaling of the pharmacokinetics of NDMA," published in 1990; is that correct?

A. Correct.

Q. And we'll have that marked as Panigrahy Exhibit 3.

Sir, in these three animal studies by Gombar, NDMA was administered to these animals both intravenously and through oral doses. Correct?

A. Correct.

Q. And many of the doses that were administered in Gombar's animal studies were massively large. Would you agree?

A. I'm not sure. You'd have to clarify what you mean by massively large.

Q. Well, let's take a look at it and see if we can maybe define it with a little more precision then.

If we start with Panigrahy-1, the beagle study. All right?

In that study, is it true that the dogs were given two doses totalling 1.5 milligrams per kilogram of NDMA intravenously? If you can look at the first page of the -- paragraph of the abstract to help you if you need to, sir.

A. Yes. IV administration was 0.5 milligram per kilogram and 1 milligram per kilogram.

Q. Right. So the total IV dose was 1.5 milligrams per kilogram. Correct?

A. No. These dogs were getting separate doses. So one set

of dogs got 0.5 mg per kg. And then a different set of dogs got 1 mg per kg.

Q. Take a look at Table 1 of that study.

A. Oh, yeah. Sorry, you're right.

Q. Okay.

A. Yeah. For the total amount.

Q. So just to be clear, the dogs in the beagle study were given intravenous doses totalling 1.5 milligrams per kilogram. Correct?

A. Correct.

Q. And in addition to those intravenous doses, each of the dogs in Gombar's study were given two oral doses totalling 6 milligrams per kilogram?

A. Yes.

MR. TRISCHLER: And I apologize, Your Honor, we have a -- these exhibits were loaded into a portal, and I don't know if they have been made available to you and to others, but there should be a way to access them. And I apologize for not pointing that out a little bit --

THE COURT: I think they're attached to his declaration.

MR. TRISCHLER: These ones are, yes. Yes, Your Honor.

THE COURT: Okay.

MR. TRISCHLER: But there may be other exhibits that

I reference that are not attached, so I just wanted to let you and Mr. Nigh and others know that there is a method to access them as we identify them.

BY MR. TRISCHLER:

Q. But in any event, I apologize for digressing there, Dr. Panigrahy.

But what I think we were getting at in walking through the methods of this dog study was that a total dose of 7.5 milligrams for every kilogram was administered to the dogs in the 1987 paper we've marked as Exhibit Number 1. Right?

A. Well, just to clarify, the total dose at one time was -- for orally was 1 mg per kg and then a different time was 5 mg per kg.

Q. Yes, we've already covered that. But the total amount of NDMA administered to these dogs in this study was 7.5 milligrams per kilogram?

A. Correct.

Q. Okay. And if we convert that to nanograms, we're talking about a total dose of 7,500,000 nanograms per kilogram being given to these dogs?

A. Correct.

Q. And would you agree with me that the average beagle weighs about 10 kilograms?

A. Yes.

Q. All right. And so if we factor in the total weight of

the animal, these dogs received a dose of NDMA totaling 75 million nanograms as part of this study. True?

A. Correct.

Q. Do you know over what period of time this 75 million nanogram dose was given to these dogs?

A. The study -- I believe it was over a month. They took a two-week break between each of the IV dose and the oral dose.

Q. Can you show me where in the Exhibit 1 the time between doses is discussed?

A. Yeah. Just looking at the Method section -- sorry.

Q. If you don't know or can't find it, I can move on for the sake of time, Doctor.

A. Yeah. I believe they say somewhere in their paper they waited about two weeks between the IV and the PO.

Q. But whatever the time period, whether it was two weeks, a month, two days, whatever the case may be, over that period of time, each of the beagles in the study received 75 million nanograms of NDMA. True?

A. Correct.

Q. Can we agree, Dr. Panigrahy, that there's no plaintiff in this litigation that ever ingested doses of valsartan-containing medications having anything close to 75 million nanograms of NDMA?

A. So when converting -- for the mechanism of action for NDMA, we don't use body weight from animals to humans. So

bioavailability, which is what this paper talks about, its entire definition of area under the curve oral versus intravenous, it's the amount of drug that will get into -- that gets into the systemic circulation. It's not -- doesn't take into account the weight of the animal.

So there are two concepts here. One is the bioavailability, which is what they're studying, which by definition is the oral NDMA area under the curve divided by the intravenous. And that doesn't -- the amount of NDMA -- actually, these doses in the dogs, 1 milligram per kilogram, IV 0.5 mg per kg IV in the oral --

(Court reporter clarification.)

THE WITNESS: Oh, sorry.

Yeah. The 1 mg per kg IV and the 1 mg per kg and 5 mg per kg orally are actually in a dog quite low.

We do animal experiments in multiple species, in rabbits, in goats, in mice, and that 1 mg per kg, many people in the field would call that low.

But the mechanism of action of the cancer causation is independent of the body weight going from animals to humans.

BY MR. TRISCHLER:

Q. Doctor, respectfully, I didn't ask anything about mechanism of the action or what was an appropriate dose for a dog or bioavailability. I simply asked you if there's any

plaintiff in this action who ever ingested doses of valsartan-containing medications having anything close to 75 million nanograms of NDMA?

A. No.

Q. In fact, in your work in this case, you had an opportunity to review data and levels that were seen in the valsartan-containing medications. True?

A. Correct.

Q. And you report on that at page 10, and I think maybe page -- primarily on page 10 of your report. Correct?

A. Yes.

Q. And you -- for instance, you cite that Mylan's levels of NDMA were found to be in the range of .01 to .09 parts per million?

A. Correct.

Q. Do you remember that?

A. Yes.

Q. And if we use a dose of 320 milligrams, which is the highest dose any patient could have ever received, that high and low range translates to an NDMA level of between 3 and 28 nanograms per day. Correct?

A. Correct.

Q. And so let's say someone took NDMA in Mylan's valsartan every day for four years. The total NDMA load on -- from the low side to the high side over four years would be between

4,300 nanograms to 40,000 nanograms.

Can we agree on that math?

A. Correct.

Q. And on the other end of the spectrum, if we look at another party to this case, ZHP, and on page 10 of your report, you note that depending on the process that ZHP used, their NDMA levels were observed to range anywhere from not detected to 188.1 parts per million.

Do you remember writing that?

A. Yes.

Q. And the midpoint of that range is 94.05 parts per million. Do you agree with that?

A. Yes.

Q. And then a 320 milligram tablet, using that midpoint of 94.05 parts per million, that's approximately 30,000 nanograms of NDMA. True?

A. Correct.

Q. And so if someone were to take ZHP's valsartan for four years, and we use that midpoint level for the NDMA content, the total nanogram exposure of taking that drug every day for four years at midpoint exposure gets you around 43 million nanograms ingested over that four years. Would you agree with that?

A. Yes.

Q. So after four years of taking valsartan at those levels,

we're still almost half or a little less than half -- a little more than half of what the dogs received in this one Gombar study that you cite in your supplemental declaration. Right?

A. We're mixing two concepts here. The important part, as I wrote in my report, is that the levels of the NDMA in the contaminated valsartan are about on the average 200-fold higher than the levels that the FDA allows, than the 96 nanogram per day for NDMA.

And then in the dog study, which is bioavailability, the weight of the animal is irrelevant. By definition, bioavailability is the amount of drugs that is -- that is not metabolized by the liver and goes into the circulation. The Gombar studies address what is the bioavailability -- what is the amount of NDMA that gets into the systemic circulation --

THE COURT: Doctor, excuse me. Please stop shuffling your papers. We can't hear a word you're saying when you're shuffling your papers, please.

THE WITNESS: Sorry.

THE COURT: Thank you. That's okay.

THE WITNESS: So the body weight of the -- the amount of NDMA that is given to the dog is not relevant to the amount of NDMA that I -- in my report, I calculate the amount of NDMA in these contaminated tablets, which was on the average about 200-fold higher than the amount the FDA allows.

BY MR. TRISCHLER:

Q. Let me ask you about the swine study, which I think we've marked as Exhibit 2.

Do you have that one in front of you?

A. Yes, sir.

Q. Good. In this study, the swine were, again, dosed both orally and intravenously. Correct?

A. Correct.

Q. And the oral doses were 1.0 milligrams per kilogram and 5.0 milligrams per kilogram?

A. Correct.

Q. And according to this paper, if we look at page 1351, the first page of Exhibit 2, down in the Materials and Methods section, the average swine in this study weighted between 38 and 42 kilograms. Correct?

A. Correct.

Q. So we can use 40 kilograms as an average. You with me?

A. Yes.

Q. And just looking at the oral dose then, setting aside the intravenous dose for the time period, let's just talk about the oral dose, what this paper tells us is that the swine in Gombar's study received an oral NDMA dose of 40 milligrams followed by a second dose of 200 milligrams. True?

A. Sorry. I'm following -- the oral dose for a pig 9 to 11 is 1 mg per kg orally, and then pigs 12 to 14 were given 5 mg per kg.

Q. Okay. So some received 40 milligrams and some received 200 milligrams?
A. Yes.
Q. And talk about -- and when you do that inversion to nanograms, what's that? 200 million?
A. Sorry, I'm not following you.
Q. 200 milligrams is -- equals 200 million nanograms?
A. Right, right.
Q. So the doses of NDMA that were administered to the swine in this Gombard study or Gombar study were even higher than the doses in the beagle study?
A. Correct.
Q. And at the risk of stating the obvious, the Gombar papers involve administration of NDMA to animals at doses that are hundreds, thousands of times higher than the doses we're dealing with in this litigation. Agreed?
A. No, I don't agree, because they're mixing two different concepts. The doses that we give the animals to measure bioavailability is different from the amount of doses in the contaminated valsartan tablets.
Q. I agree it's different than the doses in the tablets. That's my point.

And you've already told us that there's no plaintiff in this litigation that ever ingested valsartan doses having anything close to 75 million nanograms, and so it only

logically follows that there's no plaintiff in this litigation that ever ingested valsartan-containing medications having anything close to 200 million nanograms?

A. So for the case of genotoxic mutagenic chemicals that are highly carcinogenic such as NDMA and NDEA, where the mechanism of action is similar in animals and humans, IARC, WHO, many agencies have said it's inappropriate to convert any type of animal weight to human weight, because the mechanism of action is through a metabolic activation through an ion.

So the weight of the beagle or the weight of the swine isn't relevant in this case to the amount of NDMA that's in the contaminated valsartan. What is relevant is the amount of contaminated NDMA, that level compared to the level that the FDA allows. And in my report, I carefully went through each of the amounts of NDMA in the contaminated tablets. And on an average it was around 187 to 200-fold increase over the FDA levels.

Q. You've said that, sir. And none of that was responsive to my question, respectfully. My only question to you was, isn't it true that no one -- no plaintiff in this case was -- took a valsartan-containing medication containing 200 million nanograms NDMA, yes or no?

A. Correct. But as I said, it's inappropriate to compare the amount of NDMA -- or the body weight of the animal compared to in the human, the amount of NDMA in the tablet.

Q. Doctor, if I could step back for a minute.

Are you familiar with the phrase "the dose makes the poison"?

A. Yes.

Q. Do you agree with that fundamental concept?

A. Yes.

Q. Do you agree that dose matters when we evaluate the toxicological and carcinogenic effects of a compound?

A. In general, the dose matters; but in the context of a genotoxic versus nongenotoxic, it depends on the type of carcinogen in this case.

Q. The dose matters whether you're talking about a genotoxic or nongenotoxic compound. Water is vital to sustain life, but if you take it in large enough doses, it can kill you. Right?

A. Right. But in a genotoxic mutagenic carcinogen as NDMA and NDEA, there's no threshold with the dose. There's no -- the FDA has established an acceptable index, but when -- that's where we have to separate genotoxic mutagenic chemicals versus non-genotoxic chemicals.

Q. When you say there's no threshold, what you're talking about is that there's no regulatory agency that has established a threshold, saying if you exceed that level, you will sustain cancer or you will sustain certain types of human cancers. That's what you're referring to. Correct?

MR. NIGH: If I may at this point, our certification

is on bioavailability, saturation and first pass metabolism. This gets way outside of -- there's numerous pages dedicated to dose. They've had ample opportunity to cross-examine him in deposition. That is not the scope of his declaration. It's bioavailability, saturation, and first pass metabolism.

THE COURT: Mr. Trischler, let's move on. Let's concentrate, please, on the certification/declaration.

MR. TRISCHLER: If I may, Your Honor, I think my last question was following up on the witness's answer, which I would think I would be entitled to do.

If I could just make perhaps a larger proffer, the -- it's the defendants' position that those matters, those matter to carcinogenicity, those matters to bioavailability, and in his declaration and in the -- that this witness has submitted, I submit that he ignores the significance of those since Daubert requires an analysis of whether the expert reliably applied science to the facts at hand.

I think that the marked differences in doses between studies and the facts in this case need to be exposed and explored. And that's what I'm trying to do. And I think that's entirely relevant to inquiry whether the methodology has been reliably applied to the facts at hand, which is part of the -- I respectfully believe, the Daubert analysis. So I think this is entirely relevant, appropriate.

MR. NIGH: Your Honor, may I respond?

THE COURT: I don't need it.

Mr. Trischler, were you able to ask during the deposition of this witness about dose?

MR. TRISCHLER: Yes, sir.

THE COURT: And in your motion, the NDEA motion, you raised the issue of exposure levels, don't you?

MR. TRISCHLER: I don't have the motion committed to memory, but I would certainly hope so, Your Honor.

THE COURT: So I think we've plowed this ground a few times. So let's move on, please. Thank you.

BY MR. TRISCHLER:

Q. One of the claims, Dr. Panigrahy, that has been made in this case by plaintiffs is that exposure to NDMA is capable of causing multiple cancers. Are you aware of that fact?

A. Yes, correct.

Q. And I have -- the plaintiffs have filed a disclosure of cancer types at issue.

Have you seen that document before?

A. I'm not sure what you're referring to.

Q. Perhaps -- I don't know if the technician has that document. It was sent to the portal. It's the plaintiffs' disclosure and designation of expert types. It might have been premarked as H. If we can mark it as Exhibit 4.

MR. NIGH: Judge, I can't see this document yet, but I have a pretty good idea what's being referred to. It's a

certification made by plaintiffs' counsel as to the various cancer types that they expect that experts may file expert reports on. I think this is irrelevant and outside the scope of Dr. Panigrahy's expert report. He has specific cancers that he opines on that are related. Whether or not it's in a certification is irrelevant by plaintiffs' lawyers.

THE COURT: Mr. Trischler, I don't have the document. And I don't know who you're referring to about a technician loading it into the system.

But what does this have to do with what he wrote in his report or his declaration?

MR. TRISCHLER: It's really simply a predicate for the question, Your Honor. I'm just trying to establish that -- that he's aware of the fact that allegation has been made that there were -- that NDMA exposure can cause cancer types downstream of the liver. That's really all I'm trying to establish by it.

I can do it without --

THE COURT: I'm sure he can answer that question, whether he's aware that the downstream cancer types are being alleged in this case.

MR. TRISCHLER: Right. That's all I was trying to do, perhaps inartfully through the document.

THE WITNESS: Sorry, yes. In my report I detail ten tumor types where I go into detailed -- actually Bradford Hill

criteria and nine different criteria of ten different tumor types, in addition to liver, nine other tumor types.

BY MR. TRISCHLER:

Q. Based on your supplemental declaration, it's obvious to me that you read the reports of defendants' expert and the Daubert challenges that have been filed.

And do you understand that it's the defendants' position that NDMA cannot cause cancers in downstream organs because of the ingested NDMA cannot escape first pass metabolism in the liver? Do you understand that to be the defendants' position?

A. Correct.

Q. And you disagree with that premise, as I understand it, and you cite the Gombar papers in support of that position in the supplemental declaration. Right?

A. Right. And also in my original report, of the 255-page report, page 77 to page 80, four pages are dedicated solely to the importance of bioavailability, which is studied in these Gombar papers.

Q. But Gombar recognizes that dose matters when evaluating the ability of the NDMA to escape the liver. Right?

A. Yes. In my report I have sections with five, ten pages at a time where NDMA and NDEA have dose responses. I cited 32 publications just on the liver cancer section alone, 32 papers where at least 10 have a dose response.

In science, you have to put it in context. So in the 580

papers I cite, if you're talking about a dose response, NDMA, NDEA do exhibit dose responses in multiple tumor types, not just liver cancer, lung cancer.

So dose does matter in -- it depends on the context.

Q. In the beagle study that we marked as Exhibit Number 1, Gombar commented on rat studies, and he observed that -- of what was classified as low doses resulted primarily in liver tumors, but high-dose administration of NDMA resulted in renal tumors. Isn't at that true?

A. Yes.

Q. And Gombar theorized that the low doses -- that at low doses, little NDMA escapes the liver, but at high doses, the liver can become saturated and a larger fraction of the dose can reach systemic circulation.

A. Right.

Q. Do you recall reading that in Exhibit 1?

A. Yes.

Q. And again, the dose at which saturation was observed to occur in Gombar in the beagle study was a single oral dose of 5 kilograms, which in the beagle we know to be 50 million nanograms. Right?

A. Correct.

Q. Gombar never predicted that saturation occurs below a 50 million nanogram exposure, did he?

A. Well, Gombar did study this. At the 1 mg per kg there

was no saturation and they calculated the bioavailability to be 93 percent.

Q. Right. So I guess I asked the question in a different way than you answered it, but I think we arrived at the same point. And that is, the only time in the beagle study that Gombar observed any liver saturation was at the 550 million nanogram dose?

A. Yes. The 5 mg per kg oral dose.

Q. And Gombar also reported in this study that DNA repair enzymes in the liver of humans were likely to be more than sufficient to prevent cancer from low-dose exposures. Isn't that true?

A. I would have to see where -- where you're referring to.

Q. Can you look at page 346 of Exhibit 1, please.

A. Yes.

Q. Gombar writes: If humans are exposed to NDMA through environmental exposure, not deliberate poisoning, the dose will be exceedingly low. Based on rat data, it would be expected that a very small fraction of the dose would pass through the liver. The ability of the human liver to repair a lesion such as O-methylguanine should be sufficient to substantially reduce the risk of liver cancer from this type of exposure. Correct?

A. Right. They're citing a paper, reference 36.

Q. Right. And there's nothing in Gombar's beagle study that

suggests that liver saturation is going to occur at doses as low as 150 nanograms, is it? Is there?

A. Sorry, I didn't follow the question.

Q. I apologize if it wasn't clear.

What I was asking is, there's nothing in Gombar's beagle study that would suggest or support the proposition that liver saturation in the human is going to occur at doses like 150 nanograms or a 1,000 nanograms or even 10,000 nanograms?

A. So by definition, bioavailability is -- doesn't calculate saturation. There are two different concepts that are being mixed here.

Bioavailability by definition is just the amount of NDMA that gets past the liver unmetabolized and gets into the systemic blood flow and can cause cancer throughout the body.

Q. All right. Well, that's -- that's fine. But it wasn't, respectfully, responsive to my question.

I think what I asked you was, the only time -- I asked you about saturation, not bioavailability. I think I understand that there's a difference.

And the only time Gombar observed saturation was at the high dose of 5 milligrams per kilogram. Correct?

A. Correct.

Q. So there's nothing in Gombar's study that you brought to the attention to the Court in your supplemental declaration to suggest that the human liver becomes saturated if it receives

a dose of NDMA of 1,000 nanograms or 10,000 nanograms or even 100,000 nanograms. True?

A. It's not relevant here. The saturation at the high dose actually has higher bioavailability. What Gombar has studied at the 1 mg per kg dose where they calculated 93 percent bioavailability, there was no saturation.

Bioavailability is independent of the saturation. By definition, it's -- I won't go into it's area under the curve, it's just when you give the NDMA orally versus when you give it intravenously, which by definition, you get 100 percent. Saturation is just the amount of extent a chemical can be either solubilized or permeabilized. Saturation is a different definition from bioavailability. Gombar was addressing what the bioavailability is here.

MR. TRISCHLER: Your Honor, I'm going to object and move to strike as nonresponsive. I don't think I've gotten an answer to the question of whether there's anything in this paper that would allow a research scientist to conclude that the human liver becomes saturated at doses of NDMA below 100,000 nanograms.

MR. NIGH: Your Honor, if I may, our certification never says that we need to have saturation in order for NDMA to get past the liver. Our certification is clear that all it takes is bioavailability, even without saturation. That's his opinion. 49 to 93 percent gets past the liver without

saturation. That's what we're trying to make clear in the declaration. And Mr. Trischler keeps going on to when it's going to be saturated and how much does it take to be saturated. That's not his declaration opinion. 49 to 93 percent gets past the liver without saturation.

THE COURT: Well, clearly he's trying to say that saturation is irrelevant to the amount of NDMA that enters the human bloodstream. But to Mr. Trischler's point, that whether or not this Gombar study means that human livers can be saturated at the low levels, the relatively low levels, relative to these animals, of NDMA ingestion is his precise question.

I agree that it doesn't have a whole lot of relevance, but that's his question, and the witness hasn't answered that yet.

Doctor, can you answer the question about saturation of human livers and whether you can take anything from the Gombar study regarding saturation? I understand your point about bioavailability, but the question's about saturation.

THE WITNESS: Oh, sorry. I missed the -- so, yes, we cannot -- in the -- we can't conclude from the 1987, this particular study, what amount in the human would saturate the liver.

But what we can conclude, if we jump to the -- I think this is where you're getting at is what would be the

bioavailability in humans, what would be -- and that's addressed in the 1990 Gombar paper I cited.

THE COURT: Well, that's not what Mr. Trischler is getting at at the moment. He's focusing on saturation. I understand your point, though, about bioavailability, but let's just focus on what Mr. Trischler is asking, which is about saturation at this time. Okay?

Thank you.

THE WITNESS: Sorry, just to clarify the question again. I missed it.

MR. TRISCHLER: I'll reask it.

THE COURT: Please.

BY MR. TRISCHLER:

Q. There is no -- nothing in the beagle study that would support a conclusion that the human liver becomes saturated at relatively low levels of NDMA exposure on the order of 10,000 to 100,000 nanograms, is there?

A. Correct.

Q. Now, are you familiar with the work of Professor Maria Diaz Gomez on the pharmacokinetics of NDMA?

A. Yes. I did -- you know, I cited one paper with -- she was a co-author, and there's several papers. I'm not sure which one.

Q. Well, I was referring to the papers that Gombar cites to that we've marked as Exhibits 1, 2 and 3.

Have you read the papers of hers that are cited by Gombar in his work?

A. Yes. There's several papers. I have the one, actually, right in front of me. 1977?

Q. I think so.

A. Yeah. Yep.

Q. Okay. And isn't it true that Dr. Gomez reported that when orally administered, liver prevents nitrosamines from reaching other organs?

A. Yes. And this is consistent with my report where low doses can get metabolized by the liver, and at higher doses, the NDMA gets past the liver and you can get other cancer types.

Q. And so far in the papers that we've talked about, the high doses getting past the liver have been defined as -- by Gombar as 5 milligrams per kilogram. Correct?

A. No. The 1 mg per kg, the low oral dose, is what they used to calculate the bioavailability, not the 5 mg per kg. And at that low dose, there's no saturation. And the bioavailability in the dogs was 93 percent, you know, swine, 67 percent.

Q. In the Diaz Gomez paper that you read and that Gombar cites to, the scientists in that paper write that: These experiments would imply that in a healthy man, the metabolism and activation of NDMA in the diet would take place in the

liver, and that the liver would remove the nitrosamine from the portal blood and prevent it from reaching other organs.

Do you agree with that?

A. I'm sorry. I'm just getting to -- what page?

Q. 499, sir.

A. Yes. Which paragraph?

Q. It's in the bottom right-hand column, last paragraph.

A. Yes. I see it.

Q. Do you agree with that statement, sir?

A. That can happen in a certain -- what I wrote in my report is that -- so we don't rely on one paper. In certain papers, NDMA can cause liver cancer, but in other papers, the NDMA can cause kidney cancer and many other types. And that's -- by definition, the NDMA is getting past the liver.

And in science, we don't rely on two, three papers. When I cited all these papers and, for example, the Anderson paper, which is a 1994, oral NDMA in a monkey caused DNA adducts in 32 different tissues. So that's an important finding, that in a species that's similar to humans, that one single dose can get past the liver and cause DNA adducts, which is one of the initiators of the mechanism, how it causes cancer, in 32 different tissues.

So, yes, there are papers, and I do agree with the sentence that at low doses in certain papers NDMA in a rodent can cause liver cancer, but then I cite other papers where

NDMA in the mouse or the rat or rodent can cause other tumor types, like kidney cancer.

In fact, this is an important point, that when a chemical is multi-species, multi-organ by different administrations, that's when -- and it's genotoxic, that's why this chemical has been studied in hundreds of papers, which I cited. So we don't rely on just one paper on this.

Q. Sir, I don't think -- somewhere in there, there might have been an answer to my question, but if there was, I missed it, so let me try again.

All I asked you is if you agree or disagree with this statement, quote: If man and the rat are comparable, these experiments would imply that in a healthy man, the metabolism and activation of NDMA in the diet would take place in the liver, and the liver would remove the nitrosamine from portal blood and prevent it from reaching other organs.

That was the conclusion from Diaz Gomez.

Do you agree with it?

A. No, I don't. Because as I cite in my report, the NDMA given in a rodent can cause other tumor types. If we only saw one tumor type, I would agree with this comment that, yes, the liver is the only organ that can metabolize NDMA, but we know NDMA in rodents causes a -- and I wrote in my report at least seven different type of tumor types that are beyond the liver.

So in discussions you can say anything you want in a

scientific paper. Usually peer reviews are more critical on the data generation. So to back up a sentence like that, I would have to see a peer-reviewed paper to support that.

Q. Did you also read the -- well, isn't Professor Diaz Gomez's paper published in 1977 peer reviewed?

A. Yes, yes. No, but I --

Q. And her statement would have been peer reviewed?

A. Right. So where I say we don't rely on one paper in science, like, for example, I gave -- I'll just give one paper example, the Anderson paper that I cited, 1994, that an oral administration of NDMA in the monkey, which is genetically closer to a human, induced 32 different tissues to have DNA adducts.

So by definition, when you get DNA adducts beyond the liver, that's showing absorption and excretion and bioavailability in an indirect way. The Gombar studies bioavailability directly by measuring the concentration. But there are indirect measures in science.

And so, yeah, that's where I say this one sentence, I actually support -- certainly, papers that I cite in my report do support that NDMA causes liver cancer. In fact, I cited 32 publications in the liver section part that NDMA causes liver cancer. But you can't ignore the other papers that NDMA can cause other types of cancers, like seven different types of cancers in ten different species via six different

administration methods.
Q. I didn't -- sir, I didn't ask you about cancer causation. All we're talking about is metabolism right now. I thought you knew that.
But since you brought it up, this Anderson paper that you've mentioned, can you give us a citation to that whole paper, please?
A. Sure. It's actually reference 121 in my -- it's reference 121 in my report on page 228.
Q. Okay. And what was the dose that was given to the monkeys to induce cancer in that study?
A. Let's see. I have to -- I believe it was on the order of 1 mg per kg or 0.1 mg per kg.
Q. Well, why don't you take the time to look at it, because I'd like an answer that we can rely on.
A. Sure.
THE COURT: While we're waiting, for the court reporter, Ms. Mitchell, when the witness testified adducts DNA, it's A-D-D-U-C-T-S, adducts. Okay?
THE TECHNICIAN: Good morning or good afternoon, everyone, depending on where you are. This is James Budkins, your concierge for today.
THE WITNESS: So the dose, adult monkeys received 0.1 mg per kg NDMA orally by gavage.
BY MR. TRISCHLER:

Q. And is this study called "NDMA derived O-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol"?
A. Yes.
Q. That's a mouthful.
A. Yeah.
Q. Glad I was able to spit it out.
But in this study what was done was that alcohol was administered to the monkeys in addition to NDMA in order to defeat the DNA enzymes of that mammal. Correct? The DNA repair enzymes of that mammal, I should say.
A. Correct. In some of the monkeys, they did receive ethanol too.
Q. Right.
A. Yes.
Q. So going back to the issue that I wanted to talk about, because I thought this is what your supplemental declaration dealt with, where the Gombar papers and the materials that were relied upon by Gombar to determine whether or not there's a scientific basis to support this idea of -- about NDMA's ability to cause cancer downstream of the liver. Are you with me?
A. Yes.
Q. So we were talking about the Diaz Gomez paper.
Another paper that Gombar cites is the paper by Mico,

M-I-C-O. Do you remember reading that paper?
A. Yes.
Q. I think you also cited to that paper in your own report. Correct?
A. Correct.
Q. And just like Diaz Gomez, Mico and his colleagues reported in their study that the results support the previous conclusion that the liver is the site of NDMA-induced lesions after low chronic doses because it is the virtual -- it is virtually the exclusive site of metabolism after oral administration. Isn't that what Mico found?
A. Well, Mico did find that the bioavailability in the rodents are in that 8 to 10 percent range. And that's what Gombar does cite in the Gombar papers. And that's an important concept, that in the animals with lower body weight, the rodents, that the bioavailability was only in that 8 to 10 percent, and that in the higher animals, the swine, the dog, the monkey, the bioavailability was almost 12-fold higher than the rodents, even though all the species -- the seven species they studied had very high clearance. So that's a very important point. And this gets back to because obviously -- because NDMA is a human carcinogen, we can't test it in animal -- in humans.

And so the third paper that I cited for the declaration, which we may get to, that's where they actually do cite the

Mico paper. And Figure 3 has an extrapolation between the mouse, the hamster, the rat, and then the pig, the swine, and the monkey.

And that -- that's where -- the bottom line, as I wrote in the declaration, the larger animals have higher bioavailability, up to 12-fold higher than the rodents.

And this would argue and suggest that NDMA in larger species, including human, would have much more systemic bioavailability of NDMA and it can get past the liver.

Q. Is a pig a good comparison to the human?

A. So I actually did cite in my report that a pig -- there are a lot of advantages. The pig has a similar cardiovascular system, similar immune system, similar physiology as humans. So in certain ways, a pig would be better than a rodent.

Q. Okay. But let me focus on Mico for a minute.

Do you have that study?

A. Let me see. I can probably pull it up on my computer. I don't have a printout.

MR. NIGH: Is this an exhibit that you're using? Because he doesn't have this printed out. And if we're going to use this as an exhibit, I'd like a copy of the exhibit as well.

MR. TRISCHLER: Yes. I can mark it as Exhibit E, Mr. Nigh, if you'd like. And there should be an ability to -- I don't know if our concierge has that ability, but there

should be an ability to display it.

THE WITNESS: I do have the paper on my computer.

BY MR. TRISCHLER:

Q. All right. Then in the interest of time to try to move forward, if you have the paper in front of you --

MR. TRISCHLER: And I apologize, Mr. Nigh, that you don't have it. If you want --

MR. NIGH: I would object. If we're using an exhibit, he didn't print out 600 page -- you know, every single exhibit in his expert report. If we're using it, I believe I'm entitled to a copy.

MR. TRISCHLER: I don't disagree.

Your Honor, may we take a recess so I can figure out how I can get the exhibit to Mr. Nigh? I'm not as proficient with remote procedures as I should be.

THE COURT: Somebody came -- yes, the answer your question, sure.

But somebody came on as a concierge.

Who set that up?

MR. TRISCHLER: I thought it was set up to assist in providing the exhibits and presenting them.

THE COURT: We didn't. The Court didn't set that up, so --

MR. TRISCHLER: We did. The defendants did.

THE COURT: Okay. Well, then why don't you get in

touch with your concierge and find out if we can get this stuff up. We'll take a little break.

MR. TRISCHLER: May we take five minutes to figure out some administrative issues?

THE COURT: Sure.

(Recess at 12:07 p.m. to 12:24 p.m.)

MR. NIGH: Can I raise my objection to showing the Mico. The declaration clearly mentions the Gombar study and the human -- I mean the pigs, the monkeys and the dogs being the larger species, and Panigrahy's opinion being that the bioavailability would be the similar to the larger species, not the rodents. And I see that we're going to be showing another rodent study. This is outside of his scope. His opinion is based on larger species compared to -- in larger species being similar to the human.

MR. TRISCHLER: The Mico study is cited by Gombar. The witness has cited to 268 animal studies in his report, over 150 of which involve rats and rodents. Considering that this is a paper cited in -- cited by Gombar, I think it's directly probative of the issues of bioavailability, saturation and metabolism of NDMA.

THE COURT: I'm not familiar with the Mico study, Mr. Trischler.

How about the Reader's Digest version of it. What does the Mico study say in your estimation?

MR. TRISCHLER: Essentially what the Mico study says is that at low doses, the liver is the site of metabolism of NDMA and --

THE COURT: Why can't we ask the witness that question, whether he agrees or not with that?

MR. TRISCHLER: That's what I was trying to do. I was going to refer to a specific statement when we got sidetracked by trying to find the document so that the witness could see the statement that I was going to ask about. But --

THE COURT: Why don't you just read him the statement and ask if he agrees or disagrees with it and what his reasons are and we'll go with there. Why do we need to spend all this time trying to find this thing?

MR. TRISCHLER: Very well, Your Honor.

MR. NIGH: Your Honor, there is over 90 to 100 different studies that are cited by Gombar and there's over 600 studies cited in his expert report. I don't think that's a basis to say that's within the parameters of his declaration. His declaration is much more limited than that.

THE COURT: It's a very limited declaration. It's about saturation and bioavailability and how bioavailability is not dependent on saturation. I get it. But I'm going to let him ask this question about -- because we have talked about the relative size of the animal and that effect on the bioavailability of NDMA.

So go ahead, Mr. Trischler, ask your question.

MR. TRISCHLER: All right.

BY MR. TRISCHLER:

Q. Dr. Panigrahy, referring to the Mico study, do you agree that the authors of the Mico paper concluded that at low doses the liver is the site of metabolism of NDMA?

A. Yes.

Q. Have you -- now, have you read all of the work by Gombar and his colleagues on the subject of the pharmacokinetics of NDMA?

A. I've read the three Gombar papers, if you're asking, the three papers that I cited in this declaration, so yes.

Q. Are you familiar with the paper by Harrington entitled "The Formation, Disposition and Hepatic Metabolism of NDMA in the Pig"?

A. Which reference are you -- I don't know that offhand. Which reference are you...

Q. It's cited -- it's a paper by Harrington cited in the Gombar papers that you have mentioned in your declaration.

A. Which of the three Gombar papers? And I can probably find the reference.

Q. Let me show you the first page of the document and see if it refreshes your recollection.

James, can you display that, please?

THE TECHNICIAN: Yes, no problem. This is J which

will be 5. Correct?

MR. TRISCHLER: 6, but --

THE TECHNICIAN: This is the Mico. Correct?

MR. TRISCHLER: 5 is Mico. This is Harrington.

THE TECHNICIAN: Harrington.

MR. NIGH: Judge, I would renew my objection. I don't see how it's fair, even for foundational questions, to show a document that's not being provided to the witness as a whole copy or to Your Honor or to myself.

Judge, you're on mute.

THE COURT: Thank you.

Doctor, this is I think the swine study, and it's note number 8 I think is the Harrington paper he's referring to? I think. Harrington, McGee.

MR. TRISCHLER: Yes, Your Honor.

THE COURT: Can you see that, Doctor?

THE WITNESS: I see reference 8, yes.

THE COURT: Are you familiar with that paper?

THE WITNESS: Yeah. I think in the thousand publications over that I reviewed, I did remember, you know, this could have been one of them.

THE COURT: Okay.

BY MR. TRISCHLER:

Q. In Harrington, the lead author on this paper, Exhibit 6, Harrington is actually one of the co-authors of the three

Gombar papers that we've been talking about. Correct?

A. Right.

Q. And if I can direct your attention to this paper, you've already told us that the pig is a good model for the human. If we look at page 627 of this paper, we see three graphs on the bottom right side of the document.

MR. NIGH: Judge, now we're actually using the document. I'm going to object to this because my witness doesn't have a copy of the document. It sounds like we're going to start selectively choosing a few phrases, and the doctor doesn't have the context around it, neither do I, and I don't believe Your Honor has it either.

MR. TRISCHLER: The doctor has already said he's read it and he's familiar with it. If he needs time to review it, we can provide him the time to review it. But I think it's fair cross-examination of a paper by the same authors who wrote the papers on which he's relying upon.

THE COURT: Mr. Trischler, what's the point? Where are we going with this?

MR. TRISCHLER: The point, this paper, I believe, contradicts his conclusions concerning the pharmacokinetics of NDMA.

THE COURT: You have experts who directly contradict his conclusions who cite other papers. So what? I'm aware of that.

Unless you think you can get him to recant, completely recant his declaration, there's no point to this. It's not helping me at all.

MR. TRISCHLER: I want -- fine, Your Honor. If the ruling is that I can't cross-examine on the document, I'll respect the ruling.

THE COURT: Well, nobody has it. It's going to take us hours apparently to get it and have everybody have an opportunity to look at it.

So I'm going to sustain the objection. Let's move on.

BY MR. TRISCHLER:

Q. You have embraced the -- Professor Gombar's work and findings in these three papers that we have marked as Panigrahy-1, -2 and -3. Fair to say?

A. Correct.

Q. And -- but given species to species differences, the differences in doses between animal studies and humans and other factors, do you agree that Professor Gombar and others have repeatedly cautioned against using animal data like this to extrapolate carcinogenicity to humans?

MR. NIGH: I'm going to object. This is going outside the scope. Carcinogenicity is not bioavailability, it's not saturation, it's not first metabolism. We're going outside the scope again.

THE COURT: Mr. Trischler, what does this have to do with saturation and bioavailability, which is the subject of this declaration?

MR. TRISCHLER: It's right in the papers that he cited that are in his declaration that --

THE COURT: Well, that's not -- first of all, that's not what he cited the papers for.

Second of all, I've already addressed this on Monday. I understand and we all understand and all scientists understand the difficulties in extrapolating human studies -- I mean, animal studies to humans. That's a given. We all get that. And it's got nothing to do with bioavailability and saturation. Let's move on.

BY MR. TRISCHLER:

Q. You agree that Gombar has admitted it himself that proof of NDMA as a human carcinogen is lacking?

MR. NIGH: Again, outside the scope.

THE COURT: Sustained.

MR. TRISCHLER: Your Honor, if I may make a proffer, the doctrine of completeness, if a witness relies on a study, you should be permitted to introduce evidence of other relevant information in the same study that the witness is relying upon.

THE COURT: Counsel, you're forgetting where you are. This is not a jury. This is me trying to answer the questions

raised in your motions, the very, very limited role that I have. This is not helping me decide your motions.

I understand that there's weaknesses in all the reports. I understand -- and both sides have pointed them out very well, which I tried to say the other day. I get all that. This is not an opportunity to refile your motions, reargue your motions. This is not a jury who is going to determine who has got the better witnesses. This is not a jury who is going to determine whether or not a particular expert should or shouldn't have relied heavily on a particular study. That's not what we're doing here.

Focus on the declaration, please. Thank you.

MR. TRISCHLER: Understanding the Court's ruling, I have no further questions.

THE COURT: Mr. Nigh, any questions?

MR. NIGH: Briefly, Your Honor.

CROSS-EXAMINATION

BY MR. NIGH:

Q. Doctor, do you have your declaration in front of you?

A. Yes.

Q. And did you read page 11 of the defendants' reply brief wherein they criticized your opinions because you did not state the level of NDMA required to saturate the liver?

A. Yes.

Q. Doctor, can you explain what bioavailability means?

A. Yes. I defined it in the document number 4. Bioavailability is the percentage of the NDMA dose that will pass the liver without being metabolized and thereby be available in the systemic circulation.

Q. Doctor, how does saturation relate to bioavailability?

A. Saturation is the -- by definition is the extent where NDMA could be solubilized or permeabilized. The definition of bioavailability is independent of saturation. So there are two concepts that the defendants are conflicting -- conflating.

Q. Doctor, once the liver is fully saturated, what percentage of the remaining dose becomes bioavailable?

A. Then 100 percent will become bioavailable.

Q. Doctor, does the liver need to be saturated before bioavailability can occur?

A. No, it does not, and that's why I cited the three Gombar papers. At the low oral dose, there's no saturation, yet there's high bioavailability.

Q. And Doctor, does the liver need to be saturated before some of the substance gets past or a percentage of the substance gets past the liver?

A. No.

Q. Why not?

A. Because by definition, the systemic bioavailability is the amount of the chemical, in this case NDMA, that gets into

the systemic circulation, and that's independent of that saturation.

Q. And Doctor, specifically for NDMA, does the liver need to be saturated for NDMA to get past the liver?

A. No.

Q. Why not?

A. Because the blood will flow -- you'll have a -- there's no 0 percent bioavailability. Even in the rodent, which is 8 to 10 percent, a certain amount of the NDMA can get past the liver. So the bioavailability -- again, I define it, it's the amount of drug that gets past the liver. And that's, as I said before, the area under the curve through the oral delivery divided by the intravenous. It's just the definition that's independent of saturation.

Q. Doctor, are there any studies that support the idea that NDMA gets past the liver regardless of whether the liver is saturated?

A. Yes. So the Gombar papers I cited, they clearly show at the low oral dose, at the 1 mg per kg, there's no saturation. And in the swine, there is 67 percent bioavailability. In the dog -- beagle study was 93 percent, again, at the low oral dose where there's no saturation. And then in the monkey, there was 49 percent bioavailability, independent of the saturation.

Q. So did the Gombar studies support that for the dog,

93 percent of the NDMA is getting past the liver and into the bloodstream?
A. Yes.
Q. Doctor, and that's before saturation. Correct?
A. Right.
Q. If it were saturated, the liver -- then saturated a higher amount gets past the liver than the 93 percent in the dogs. Correct?
A. Correct. And that's what Gombar showed. Actually at the higher doses where there was saturation at the 5 mg per kg orally, the percent of bioavailability was even higher than the 93 percent in the dog and the 67 percent in the swine.
Q. Doctor, did the Gombar study author suggest any differences in the amount of NDMA that gets past the liver between larger animals versus smaller animals?
A. Yes. These studies would suggest more NDMA would get in the systemic circulation in a larger species such as the dog, swine, and pig. And they suggest in their 1990 paper that a human would be more like a larger species, so it would have higher bioavailability than a rodent.
MR. NIGH: I don't have any further questions, Your Honor.
THE COURT: Mr. Trischler, do you want to ask any questions about that?
MR. TRISCHLER: No. Thank you, sir.

THE COURT: All right. Thank you.

All right. What's the status on the next witness? Do we need to take a -- it's 12:43. Can we start, and then if we have to break, because Ms. Brown needs to go? Do you want to start, Ms. Brown, with the next witness?

MS. BROWN: I completely defer to the Court, Your Honor, whatever is best. I was going to ask for a few minutes with the tech person to just see if I can get my Elmo working so I myself could show a document and save us trouble. But if Your Honor's preference is to just keep going, we can do that too.

THE COURT: Well, let's take a 10-minute break and then try to get set up and get the witness --

MS. BROWN: I appreciate it.

THE COURT: -- who's somewhere far away, I think I remember. So let's get the witness. We'll take ten minutes. Okay? Thank you.

MS. BROWN: I appreciate it, Your Honor. Thank you.

(Recess at 12:42 p.m. until 12:50 p.m.)

THE COURT: All right. I don't want to butcher your name. Etminan?

THE WITNESS: That's right.

THE COURT: Dr. Etminan, would you raise your right hand, please.

MAHYAR ETMINAN, PharmD, MSC, PLAINTIFFS' WITNESS,

after having affirmed, was examined and testified as follows:

THE WITNESS: Yes.

THE COURT: State your full name, sir.

THE WITNESS: Mahyar Etminan.

THE COURT: All right. The lawyers are going to ask you some questions. Let's get started.

MS. BROWN: May I proceed, Your Honor?

Thank you.

DIRECT EXAMINATION

BY MS. BROWN:

Q. Good afternoon, Dr. Etminan. How are you?

A. I'm good. Thank you.

Q. My name is Alli Brown, and I have some questions for you on behalf of the folks at ZHP and the other defendants. Okay?

A. Okay.

Q. All right. And to set the stage, Doctor, I understand that in this case you've written a report, and you are of the opinion that exposure to NDMA and NDEA can cause nine different types of cancers; is that right?

A. That's right.

Q. Okay. And the methodology, Doctor, that you used to form that opinion, as I understand it, was a systematic search of the scientific literature and a systematic appraisal of the available evidence. Does that sound familiar, sir?

A. Yes.

Q. Okay. And essentially what you did, Doctor, is you conducted a literature search. Correct?
A. That's right.
Q. Okay. And then you performed a Bradford Hill analysis on a subset of the literature that you looked at. Is that fair?
MR. VAUGHN: Object to the scope, Your Honor.
If I may explain myself.
THE COURT: Sure.
MR. VAUGHN: Dr. Etminan's entire declaration is just him explaining and providing evidence of how the defense took a partial quote from his report out of context. The scope of his cross should be limited as to whether he was taken out of context and if the contents of his declaration are the correct context. Allowing the defense to revisit topics which they have already extensively deposed Dr. Etminan on will only reward and incentivize their tactics.
THE COURT: No, I understand. And we're not getting far afield. Don't worry about it. But I think some background information is certainly relevant here as to how he arrived at his opinions, and then we'll move into the declaration.
MR. VAUGHN: Thank you, Your Honor.
THE COURT: Go ahead.
MS. BROWN: Thank you, Your Honor. Appreciate it.
BY MS. BROWN:

Q. So just to reorient us, Dr. Etminan, after doing the literature search, I understand you did a Bradford Hill on a subset of some of the literature you found. Right?
A. I did a Bradford Hill on the studies or the evidence that met my inclusion criteria that are laid out in my report, yes.
Q. Understood, sir. And what you mean by that is you determined what studies to include and what studies to exclude in your Bradford Hill. Is that fair?
A. That's right.
Q. Okay. And to be fair, Doctor, and it's the subject of your declaration that we're getting to right away, you didn't give all of the studies the same amount of weight in your analysis. Is that true?
MR. VAUGHN: I'm going to relaunch my objections to scope.
THE COURT: Well, I understand that, but I think it's pretty obvious that none of the experts in this case or any case ever gives equal weight to all the studies.
MS. BROWN: I understand.
THE COURT: I think we can all guess at what the answer is, but go ahead.
MS. BROWN: Thank you.
THE COURT: Let's move along.
BY MS. BROWN:
Q. And that's true, right, Doctor, is that you made a

determination about what weight to give to what studies. Correct?
A. That's right.
Q. And that was part of your methodology. Right?
A. Correct.
Q. Okay. And in your declaration in this case that we're here to talk to you about, you talk about two studies that you gave little weight to. Right?
A. That's right.
Q. Okay. And what you tell us in your declaration at paragraph 3 is that you gave little weight to studies called Gomm and Pottegard; is that right?
A. Correct.
Q. Okay. And in terms of all the studies cited in your report, those are the only two studies that evaluated exposure to NDMA and NDEA from valsartan, the medicine. Right?
A. That's right.
Q. Okay. And the other studies you relied on, sir, were occupational or dietary studies. Is that true?
A. True.
Q. Okay. And neither of the two studies, Gomm or Pottegard, that you gave little weight to, neither of those two studies found an association between exposure to the medicine valsartan and overall cancer risk. Right?
A. Generally speaking, yes, although they did show some

increase in risk of some cancers, but globally, even they looked at all cancers. I believe Pottegard showed a very small increase in risk that was not statistically significant, and Gomm I believe showed an increase in risk with liver cancer only.

Q. So in terms of the analysis, though, of whether exposure to these compounds from the medicine valsartan increased the overall risk of cancer, both of these studies found no association with the overall risk of cancer.

Would you agree with that, sir?

A. Again, I'd like to be a bit more specific.

With Pottegard, they do report a 9 percent increase in risk that was not significant statistically; nevertheless, they do present a 9 percent increase in risk.

Q. And, actually, though, when Pottegard reports that nonstatistical finding, they report it as no association with an overall cancer risk. Right, sir?

A. That's what they report.

Q. Okay. And when you say in your declaration, that that's the issue of the question in here, sir, you say that you gave these studies little weight, because in your view, these studies were what you call inconclusive. Right?

A. I came to the conclusion that they were inconclusive as a result of a number of limitations that I also discuss in detail.

Q. Okay. And the word "inconclusive," that's your word. Right? The word "inconclusive," it doesn't appear in either of those articles. Correct?
A. That's my word, yes.
Q. Okay. And, in fact, Doctor, you wrote a letter to the authors of the Pottegard study about whether or not the study was inconclusive. Do you remember that?
MR. VAUGHN: Object to the scope. Your Honor, this is completely outside of what's in his declaration, and it's been taken out of context.
MS. BROWN: May I be heard, Judge?
THE COURT: Well, I need to know what's in the letter, to be honest with you, to find out whether this is relevant to what's in his declaration. So you can ask him about what he wrote, what was the point, what was the purpose of the letter and all that kind of stuff.
MS. BROWN: Thank you, Your Honor.
BY MS. BROWN:
Q. And so just to set the stage, Doctor, and get us all on the same page, paragraph 3 of your declaration, you tell us that these two studies were inconclusive in your view. Right?
A. Yes.
Q. And that's why you gave them in your analysis little weight. Correct?
A. Yeah.

Q. Okay. And the idea of whether or not the Pottegard study was inconclusive or not, as you say in your declaration, that's something that you've actually raised with the author of the Pottegard study. True?
A. I remember that I did write a letter. I don't remember the details, but I did read -- write a letter, yes, bringing up some of the points that I also bring up in the report regarding the study.
Q. Okay. And what I'd like to do is hope -- we'll see if we can do it, but hope that I can share my screen.
We'll mark as Etminan-1 a copy of that letter. And I'm going to see if I can show it to everyone here.
Okay. So can everyone see that? Most importantly the Judge and you, Doctor?
A. Yes.
Q. Okay. Terrific.
All right. And so let's just orient ourselves about -- this letter is coming from you in September of 2018. Right, sir?
A. Yes.
Q. Okay. And you're writing this letter to the author of one of the two studies that you determined was inconclusive, and therefore, you gave it little weight. Right?
A. That's right.
Q. Okay. And the title of your letter to the author

actually uses the word "inconclusive." Right, sir?
A. Yes.
Q. What you title your letter is: Epidemiologic Study of NDMA-Contaminated Valsartan Use and Risk of Cancer, Reassuring or Inconclusive? Right?
A. Yes.
Q. And you had a series of comments about whether or not the findings were reassuring or inconclusive that you asked the authors about. Right?
A. Yes.
Q. And there were some other folks who also sent some letters. Right?
A. Yes.
Q. Okay. And you know that the authors responded to you. Right?
A. Yes.
Q. Okay. And in the authors' opinion, sir, in answering the question you raised, are the findings reassuring or are they inconclusive, the authors actually told you and others that they were -- the findings were reassuring. Right?
Let's take a look at what they said.
This is from around the same time, from the Pottegard author responding to your letter and somebody else's letter. And the authors say: While we can't rule out a small increase even several magnitudes larger than the one estimated by the

FDA, our estimates do provide some reassurance that no major increase in cancer incidence could be detected.

Do you see that?

A. Yes. That's their opinion. Yes.

Q. So as to the question you raise to the very authors of the study, are they inconclusive or are they reassuring, the authors, the folks who wrote the study, believed the results were reassuring. True?

A. That's what they say, yes.

Q. Okay. And they also answered directly, sir, some of the issues and critiques that you raise in your declaration. Isn't that right?

A. If you could put it back. It's been a while since I saw that letter, so if I could just --

Q. Absolutely. Fair enough, sir. Let me help orient us a little bit.

I'm going to your declaration here to get us oriented to another critique you tell us in your declaration and a critique that you raise with the authors --

A. Sorry, can I see the response from the authors again? That's what I meant.

Q. Oh, sure. Absolutely, sir.

A. Thank you.

Q. I don't know if we can put it in the chat so that -- okay.

This is what we were looking at, Doctor, the response from the author. Right?

A. Okay. So can I just have a few minutes just to read the whole response?

Q. Oh, yeah, absolutely. And there's another response I want to show you.

This is a response to Dr. Zhou that we were looking at. He's the other author attached here. And then there was a specific response that I wanted to show you, addressed to yourself. Okay?

A. Okay. Can I then just -- if you want to ask me about the responses, can I read them all, please, and then --

Q. Absolutely. Absolutely. What I want to ask you about is what I have highlighted here, which is a response to you specifically. And I'll just put it up. I don't know if I can zoom it in. If you want a minute, just tell me when you're ready to go to the next page.

A. Okay.

Can you please flip the page?

Q. Sure thing. Absolutely.

A. Okay.

Q. So one of -- going back to your declaration that's the subject of our questioning here today, in telling the Court in this declaration that you gave limited weight to these studies because you found them to be inconclusive, you listed a number

of specific critiques about the study.

Are you with me?

A. Yes.

Q. Okay. And on one of them is that the authors didn't account for the possibility that a patient could be switched from a nonNDMA-containing valsartan to an NDMA-containing valsartan during the follow-up period. Right?

A. Yes.

Q. Okay. And you also raised along the same lines the issue of misclassification of exposure in paragraph number 1. Right?

A. That's right.

Q. Okay. And that concept is actually something that you had raised when you wrote to the authors of the Pottegard study. Right?

MR. VAUGHN: I want to put an objection on the record really quickly.

I don't believe that response that you were showing was in regards to Dr. Etminan's email. And the letters that you are showing are not peer reviewed. And they're not experts in this case.

THE COURT: Well, wait a minute. I'm really worried about the first. Say the first objection again.

MR. VAUGHN: I don't believe that was a response to Dr. Etminan's email to the study authors that she was going

over.

THE COURT: Oh. Can we ask the witness if he recognizes that as the response to his letter.

MR. VAUGHN: I'm having difficulty following you, Ms. Brown. I'm trying to get the exhibits that you're using, and I'm not seeing the stuff that you're showing him.

MS. BROWN: No problem.

MR. VAUGHN: Thank you.

MS. BROWN: We can separately email it to you.

And I'll try to make it clear for the record.

BY MS. BROWN:

Q. Dr. Etminan, I'm going to direct you to a letter that was sent to you.

Dear Dr. Etminan. Do you see that?

A. That's right.

Q. Okay. And I'm going to talk to you about what the authors said.

But before we do that, I want to go back to your letter, okay, and talk about another critique that you raised with the authors themselves. Okay? Are you with me?

A. All right. Right.

Q. So one of the issues that you raised when you -- in your comment about whether it was reassuring or inconclusive, one of the things you raised is the same thing you raised in your declaration, is that it's possible that patients taking -- I'm

sorry, folks.

That patients taking NDMA valsartan may switch to other generic formulations during follow-up, increasing the possibility of exposure misclassification.

Do you see that as something that you raised with the authors?

A. Yes.

Q. Okay. And to reorient us, that's something that you raised in your declaration to the Court. Right?

A. That's right.

Q. Okay. And you raised -- you put that in your declaration to the Court as a reason why the study was inconclusive and the reason that you gave it, to use your words, little weight. Right?

A. Yes.

Q. Okay. But the authors responded to you on this exact point. Right, Doctor?

A. Can you please put back the author's response?

Q. Sure.

MR. VAUGHN: Doctor, do you have access to this entire document so you can review it in its entirety?

Ms. Brown, can you provide a copy of the entire document to Dr. Etminan and myself?

MS. BROWN: I'd be absolutely glad to. As I understand it, we're prevented from putting it in the chat.

If you want give me an email address, we can send it off right now. I do want to make sure he has the ability to look at it.

MR. VAUGHN: Mine is brett@hollislawfirm.com. I can forward it to him if you get it sent to me.

MS. BROWN: Perfect. I'm sorry. It's Brett what?

MR. VAUGHN: @hollislawfirm, H-O-L-L-I-S, lawfirm.com.

MS. BROWN: Terrific. We'll get that right to you right now.

MR. VAUGHN: And I want to relaunch the objection that this would not be competent evidence. This was not peer reviewed. These are not experts in this case.

THE COURT: They don't have to be peer reviewed or be experts in the case. She's asking whether or not his specific complaint or criticism was responded to by the author.

MR. VAUGHN: Thank you.

THE COURT: That's all we're trying to find out at this point.

MS. BROWN: May I proceed, Judge?

THE WITNESS: Well, I think you asked me a question, so can I take a couple of minutes to formulate my response?

THE COURT: You can take a couple minutes to look at the letter. You have to wait for the letter.

MR. VAUGHN: We're waiting on the letter.

MS. BROWN: As I understand it, we've sent it to you, Mr. Vaughn, so hopefully it arrives momentarily.

MR. VAUGHN: I'll let you know when I receive it.

MS. BROWN: Thank you.

MR. VAUGHN: All right. I'm forwarding it to him.

MS. BROWN: Thank you very much.

MR. VAUGHN: Let me know when you get it, Dr. Etminan. And please take your time to review the whole document.

BY MS. BROWN:

Q. Doctor, have you received the copy?

A. Sorry, how am I receiving the copy?

MR. VAUGHN: I just emailed it to you.

THE WITNESS: Okay. So if I could respond to your first point on the response of the authors to my criticism or however you like me to go about it.

BY MS. BROWN:

Q. Thanks, Doctor. I wanted to ask you a question about the critique that you raised to the authors about the potential misclassification that you also raised in your declaration.

Do you have that question in mind?

A. Yes.

Q. And in looking at the response, and now you have a copy, that came to you from the authors themselves, they address that critique. Right, sir?

MR. VAUGHN: Counsel, will you put the first page of the document up so we can see who it's actually addressed to?

MS. BROWN: Yup. Dear Dr. Etminan.

MR. VAUGHN: No, that's not the first page of the document. That's page two of the document. The response that you were going over earlier and you're acting like it was forwarded to the Doctor, is titled to Dr. Zhou. Page 1.

MS. BROWN: I don't want there to be any confusion, so I'll just address it for the record.

BY MS. BROWN:

Q. There are a number of letters, right, that you and others sent. And the letter I want to talk to you about right now is a letter addressed to you on the misclassification critique that you raised.

Are you with me on that, Doctor?

A. Yes.

Q. And it's true that what -- that what the author said was that: The ever use analyses do not introduce exposure misclassification. By definition, a patient is considered an ever user after the first NDMA-contaminated prescription fill, regardless of whether the patient uses non-contaminated valsartan later.

That was the author's response to the critique you raised in your letter and in the declaration you did for the Court. Correct?

A. That's right.
Q. And even though the authors, Doctor, responded to you on that critique, you continued to maintain that critique as a reason that you gave Pottegard little weight in your analysis; is that right?
A. That's right. Because they address my critique -- they respond to my critique but they don't really address my critique.
Q. In their view, sir, the authors believed that their paper and their research did not introduce exposure misclassification. That's what they told you, right, sir?
A. That's what they told me. But the reasoning that follows that statement is not satisfying to me, because they're basically saying, look, with respect to misclassification that you're raising, all we did was we made sure that the first prescription was a prescription that had NDMA-contaminated valsartan.

Somebody -- that same subject could have been followed later on and received a prescription with a different dose -- a different level of NDMA or no NDMA in valsartan during the follow-up of that patient. We didn't really care about that. All we cared about was that the very first prescription was NDMA contaminated.

And, again, that goes to my point that if you follow that patient who may be switching from -- you know, different

batches of the same formulation which may have different content of NDMA or different manufacturers of, say, valsartan which also may have different levels of NDMA, there is going to be measurement error in the level of NDMA in that patient's follow-up, which can introduce a bias into this study.

So to answer your question, they address my comment, but they don't really answer my comment to my satisfaction.

Q. Sir, just to be fair, you raised the issue of exposure misclassification with the authors. Right?

A. Yes.

Q. Okay. And in their response to you, they told you they didn't believe that was an issue in their study, and you disagree with the authors. Right?

A. I -- well, they explain -- they explain why there is -- there shouldn't be misclassification, but the scientific reasoning that they provide that you're showing in the letter to me is sort of counterintuitive and is not satisfying scientifically.

Q. Okay. So when it comes to the issue of misclassification or potential exposure misclassification, you have a different view of that than the authors of the Pottegard study. Is that fair?

A. I don't think we have -- misclassification in epidemiology -- if you open an epidemiology textbook, misclassification is one of the major biases that is very well

defined. What I'm saying is that the issue of misclassification that I raised is not really answered or addressed by the response that they provided.

Q. Okay. Let's move on, Doctor, and let's talk about the two reasons that you give in your declaration for why you found these studies to be inconclusive and why you give them little weight. Okay?

A. Okay.

Q. And the two issues that you raise in your declaration are, number one, that there was a short duration of follow-up. Right?

A. That's right.

Q. And, number two, what you say, most importantly, there was an inability in these studies to precisely quantify the amount of NDMA in the valsartan formulations. Right?

A. That's right.

Q. Those were your two critiques why you gave these studies less weight than other studies you reviewed. Fair?

A. I believe in my report I also discuss, perhaps, competing risk analyses, but in my declaration, yes.

Q. Right. And I'm trying to limit my questions, sir, to your declaration, so --

A. Okay. I appreciate that.

Q. -- in your declaration, you tell us about these two. Right?

A. Yes.
Q. And so I want to start with the one that you tell us is most important to you, and that has to deal with the quantification of NDMA in valsartan in these studies. Okay?
A. Okay.
Q. Okay. And the fact is, sir, is that this issue of quantification of valsartan exposure is true in all of the studies that you rely on in your report. Isn't that right?
A. The issue of quantification of NDMA, yes.
Q. Okay. And, in fact, you told us that -- you know, for example, it's an issue in the study that most of your report is based on the Hidajat -- am I pronouncing that correctly?
A. Hidajat, yes.
Q. Hidajat.
MR. VAUGHN: Object to the scope of the question. Hidajat is not mentioned anywhere in his declaration. This is getting far afield.
MS. BROWN: And, Your Honor, what is mentioned, of course, are the two critiques of the studies he gave little weight to. And I'm just exploring how that applies to the studies he did give weight to.
THE COURT: I'm not following you at all.
How could it possibly apply to the studies he gave weight to?
MS. BROWN: Well, Your Honor, the critique that he

has of two studies that he did not give weight to, right, is the same critique that applies to the studies he did give weight to, so --

THE COURT: Well, what do you mean it's the same critique? That's what I'm not understanding. What do you mean by the same critique?

MS. BROWN: Sure, Your Honor. He admitted in his deposition, that, for example, the Hidajat study also had to use estimates of NDMA exposure. And in his words, he said it's pretty much impossible to have a precise quantification, which is, of course, the critique he says in his declaration for why he gave little weight to Gomm and Pottegard.

THE COURT: Well, it's one of the reasons he cites.

MS. BROWN: Correct.

THE COURT: Okay. Well, so you want to ask him why he didn't apply the same standard to Hidajat?

MS. BROWN: Sure, Your Honor. Basically, the critique he gives the Court for why he didn't give Gomm and Pottegard the same amount of weight is a critique he admits applies to the study he gave the most weight to.

MR. VAUGHN: These are not the same critiques he even gives to Hidajat. They don't even -- they're not even able to quantify it in Pottegard and Gomm. It's a completely different critique.

MS. BROWN: I just have two questions on it.

THE COURT: Well, the Hidajat study is the subject of deposition questioning, I assume. Right? Yes?

MS. BROWN: Yes, Your Honor, it is.

THE COURT: Okay. Well, you can ask him whether or not he applied the same critique to the studies he relied on.

MS. BROWN: Understood. Thank you, Your Honor.

BY MS. BROWN:

Q. And so just to wrap this up, then, Doctor, and consistent with the Court's order, you were critical of Gomm and Pottegard for not having precise quantification of the NDMA exposure. Right?

A. Yes.

Q. Okay. But what you told us in your deposition is that that's also a problem with the study you rely on like Hidajat. Right?

A. Yes. And, again, every epidemiological study has limitations, but the Hidajat was an environmental epi study that explained in their methodology how they actually measured NDMA for their analysis. The Pottegard and Gomm studies are the only two studies that actually set out to answer this very specific question: Does NDMA in valsartan increase the risk of cancer?

So the amount of NDMA in the different dosages is the underpinning of this -- of the question that they set out to answer. And so I had a much higher expectation for these

authors to provide information, at least say they attempted to get the information on the amounts of NDMA in valsartan, which they did not do.

Hidajat was a different study with a different scope; nevertheless, they did provide the methodology that they used to measure NDMA.

Q. Okay. And that methodology, sir, was to rely on estimates of exposure, right, in the Hidajat study?

A. Yes.

Q. Okay. And you were not critical of the Hidajat author's decision to rely on those estimates. Correct?

A. Again, I did mention the Hidajat limitations. I was more critical on the NDMA amounts and concentrations in the Pottegard and Gomm studies because they -- again, this very important issue of NDMA concentration, they mainly relied on one citation that they report. And they made a -- sort of a bold assumption which we know today after knowing the information about the amount of NDMA in these dosages is not true in that they made the assumption that the higher the doses of valsartan, the higher the NDMA. So, again, I wanted to see more sort of discussion -- attempts to get NDMA-level data on these valsartan dosages, knowing that there's a huge variation between manufacturers and within manufacturers, which was not done.

Q. And one of the things both Gomm and Pottegard did to

address the issue that you're raising is they conducted sensitivity analyses. Correct?
A. Yes.
Q. Okay. And in both instances, in both studies, those sensitivity analyses produced comparable results. Correct?
A. They did. But, again, the underpinning of that sensitivity analysis was the same flaw that I raised in that they assumed that NDMA concentration goes up with increasing the dosages of valsartan, and we know that's not true. We know that high dosages of a valsartan tablet would have a lower concentration of NDMA than a lower dose valsartan. And so the assumption that they used that I criticized their results for, they used the same assumption for the sensitivity analysis, and, hence, they got similar results.
Q. Okay. Another reason, Doctor, you've been critical of Gomm and Pottegard is because you said, and you reference it in your declaration, that NDMA exposure was not specified in the control group. Correct?
A. That's right.
Q. And you told us that you would have liked to have seen the control group broken down by high exposure, medium exposure, and low exposure. Correct?
A. That's right.
Q. Okay. And the reason for that, Doctor, is because dose and duration are important to determining carcinogenicity.

True?
A. Yes.
Q. Okay. And when it comes to the compounds that are the subject of your report and your declaration and your testimony, NDMA and NDEA are found everywhere. Right?
A. That's right.
Q. They're in the air we breathe, the food we eat, everybody is exposed to some amount of these compounds. Correct?
A. That's right.
Q. And in addition to being exposed through food and water and air, our body also makes these compounds. Right?
MR. VAUGHN: Object to the scope of the question. She's getting into endogenous formation of NDMA. That's not mentioned anywhere in his declaration. They took him out of context on one quote in his expert report.
THE COURT: Ms. Brown, I'm well aware of endogenous, exogenous. It's all through all the papers. Where are we going with this?
MS. BROWN: Absolutely, Your Honor. And I'll just tie it up to the critique he raises in his declaration about the quantification. I'm not looking to replow old ground. I promise.
THE COURT: Thank you.
MS. BROWN: Okay.
BY MS. BROWN:

Q. And so, Doctor, we're not going to spend a lot of time on endogenous, but you would agree that in addition to exogenous exposure, our bodies make some amount of endogenous NDMA and NDEA as well. Right?

A. Yes.

Q. Okay. And you are critical of the two papers in your declaration, Gomm and Pottegard, for not quantifying NDMA exposure.

But the fact is, Doctor, you haven't attempted to quantify anybody's baseline exposure to these compounds. Right?

MR. VAUGHN: Object to the scope. We're going straight to endogenous formation, which is not mentioned anywhere in his declaration.

THE COURT: I'm not sure where this is going, Ms. Brown. Where are we going with this?

MS. BROWN: Understood, Judge. If I could just have two questions to tie it to the declaration, I'll move on to my next topic.

THE COURT: Okay. Let's go.

MS. BROWN: Okay.

BY MS. BROWN:

Q. And what I mean, Doctor, is even though you gave critiques about quantification in your declaration, your work in this case was not aimed at trying to figure out whether a

particular increase in exposure to these compounds increases any individual's risk of cancer. Right?

A. Can you repeat that question, please?

Q. Sure. The work that you did in this case was not aimed at answering the question about whether or not any particular increase in the NDMA or NDEA exposure that people have on a regular basis is enough to cause cancer. Right? You didn't answer that question?

MR. VAUGHN: Object to the scope again. Nowhere in his declaration does he discuss an increased risk; he was simply talking about how he was taken out of context.

THE COURT: Ms. Brown, you raised this in your motion about this baseline stuff.

MS. BROWN: Understood, Judge, and I really --

THE COURT: Do we --

MS. BROWN: Sorry, go ahead.

THE COURT: Do we have to do it again?

MS. BROWN: I just want -- I was hoping to get an answer to one question, Judge, because he raises this quantification issue in his declaration. And I just want to make clear, following up on that, that that's not even a question he looked at here.

THE COURT: I'm sorry. I didn't hear the end of that. That's not even what?

MS. BROWN: That's not even something he's prepared

to give an opinion on, Judge, meaning he didn't try and figure out what everybody's exposed to normally and whether particular increases increase your risk of cancer. His question didn't have anything to do with this -- the individual dose or exposure; he just looked at the question in general. And so the critique that he's raising in his declaration is really not tied to any opinion he even is giving in his --

THE COURT: Well, no, he's --

(Court reporter clarification.)

THE COURT: I'm sorry, Ms. Mitchell.

Go ahead. Repeat what you were saying, Ms. Brown. The court reporter didn't get it.

MS. BROWN: What I was saying, Judge, is that the critique that he's raising on the quantification of these compounds is not tied to any opinion that he's giving in this case.

THE COURT: Well, yeah, but the point of the declaration was to respond to criticisms that you, the defendants, have raised.

MS. BROWN: Yes, sir.

THE COURT: I don't think he's trying to express any new opinions here.

MS. BROWN: I understand, Your Honor.

THE COURT: Let's move on, please.

BY MS. BROWN:

Q. Let's move on, then, Doctor, to the second reason you give in your declaration for giving little weight to these two studies. And that has to do with the amount of follow-up that was covered in the studies. Right?

A. That's right.

Q. Okay. And in Pottegard, the mean follow-up was about 4.6 years. Correct?

A. The total follow-up, yes.

Q. Okay. And in Gomm it was three years. Is that accurate?

A. Yes.

Q. And you would agree that three to five years is too short a period of time to determine if NDMA in valsartan can cause cancer. Right?

MR. VAUGHN: Object. Object to the scope. He does not give any latency opinions in here. He's simply correcting how he was taken out of context and what the correct context is.

MS. BROWN: Your Honor, this is a squarely within his declaration as a reason why he disregarded two studies that show no increased risk of overall cancer with valsartan.

MR. VAUGHN: You're trying to get him to give an opinion now on how much latency is needed for individual cancers. That's not addressed anywhere in his declaration.

THE COURT: He raises the issue in paragraph 3 about

the short duration. I think he can be asked what would be an appropriate duration for a study. But you're right about latency. He's not given any opinions about latency periods for any of these cancers. But he can certainly give an opinion about what an appropriate study -- what time frame an appropriate study would encompass.

So go ahead, Doctor.

THE WITNESS: Yes. So, I mean, there is really no set sort of fixed number of years that has been agreed on as to the optimal follow-up. Obviously, cancer being a latent condition, the longer the follow-up, the more cancers that will develop. So, you know, methodologically, probably better to have longer follow-up.

But as I mention in my report, we do -- we are aware of studies of drugs that have caused cancer within a year, being promoters, cancer promoters, similar to NDMA.

So again, there is a range, the longer the better, that it could happen, you know, in a year or so, probably less likely than five years or ten years. But, you know, it is possible for a shorter duration as well.

BY MS. BROWN:

Q. Well, what you told us, sir, before, Doctor, is that three to five years is too short a period of time for cancer to develop from valsartan medicines. Right?

MR. VAUGHN: Object. Object to the scope, and you're

misstating his prior testimony.

MS. BROWN: Well, we can take a look at it. Why don't we take a look at it, Doctor.

THE COURT: Well, the Doctor can certainly tell us whether that's his opinion in his prior testimony, but I'm not sure what this has got to do with his declaration. He doesn't opine on latency periods. He just says that these studies weren't following up long enough. And you just asked him, well, how long is long enough, and you got the answer you got.

MS. BROWN: I understand, Judge. I'm just looking to test that answer against what his prior testimony was on the years, because he raised it in his declaration.

THE COURT: You can ask him what he said at his deposition or whatever about the number of years that would be ideal for a follow-up on the study of NDMA.

MS. BROWN: Thank you, Your Honor.

BY MS. BROWN:

Q. And so Dr. Etminan, you raised the objection to these studies being too short. And you told us in your deposition that three to five years is just not long enough to study --

MR. VAUGHN: Objection. You're misstating his testimony. If you're going to quote him, please put it up so we can review it.

MS. BROWN: Your Honor, could I get the question out first?

THE COURT: Are you asking him whether or not he recalls stating in his deposition that three to five years was not sufficient?

MS. BROWN: I am, Judge.

THE COURT: Doctor, do you remember saying that at your deposition?

THE WITNESS: Honestly, it was a ten-hour deposition, so no.

THE COURT: So perhaps counsel can find us a page and line number.

MS. BROWN: Sure. Sure, I can.

BY MS. BROWN:

Q. And Doctor, I'll put it up on the screen.

A. I appreciate it.

Q. If you have your transcript from 8/25, it looks like it is at page 52. And let me try to get it for you so I can help you.

I'll put it up to make it easier.

Okay. So we are at page 52 of your deposition, Doctor. And we're looking at line 5. And you were asked this question: I wasn't asking about whether there's a particular individual that might have a shorter latency period than another. I was asking about study design.

And what you told us yesterday was that a study period of four or five years, which I believe is the time frame in the

Pottegard and Gomm studies, is just too short, and it's too early to tell whether or not nitrosamines in valsartan-containing medications can cause an increased risk of cancer. You need a longer period of time to study that.

And your answer on that day, sir, under oath, was yes. Correct?

A. Yes. I mean, that is what I say. But again, going back to what I also said, the four to five years being too short, again, the sort of -- there may be some lack of context here. But too short doesn't mean that there won't be any cancers whatsoever. Too short means that optimally we like to see longer follow-ups.

And again, back to my declaration, the reasons I gave low weight to these two studies wasn't just because of the short follow-up. I list in detail a number of other limitations, the -- collectively, you know, which collectively led me to giving them a lower rate in terms of their validity.

Q. Yes, sir. And in terms of how long you would need a study to figure out whether these compounds in valsartan can increase the risk of cancer, you told us that most cancers take at least ten years to develop. Right, sir?

MR. VAUGHN: Objection. That misstates his testimony. Again, we're getting outside of his declaration. We're getting back again to cancer latency in general.

THE COURT: Well, no.

Doctor, do you remember saying that, about the ten years for most cancers to develop?

THE WITNESS: I don't. I don't remember saying that. Again, if you want to -- I could have said it. It's not something that I wouldn't have said it. But specifically in, you know, the context and when I said it or where I said it, I don't remember.

THE COURT: Okay. Well, do you agree that that's accurate?

THE WITNESS: I would -- again, optimally, the longer follow-ups, like ten years, yes, most cancers would be able to develop that -- as you know, we work with an L-shaped curve in pretty much everything, including cancer, so it doesn't mean that cancers wouldn't develop in shorter periods.

And in my report, I do talk about examples of prescription drugs that have been shown to cause cancer within a year. So, you know, it is a wide range.

MS. BROWN: And may I just show that testimony, Your Honor?

THE COURT: Sure.

I don't think he denies giving that testimony, but if you want to show it, that's fine.

BY MS. BROWN:

Q. So Doctor, we're going to page 50 of that same transcript.

And you were asked, do you know the average latency -- I'm sorry.

Do you know the latency period -- I'm sorry.

Do you know the average latency period for colorectal cancer?

And your answer was: The latency period for cancer in general is usually around, give or take, ten years.

That was your testimony under oath in August of this year. Right, sir?

A. Yes. I mean, general that I stand by that.

Q. Right. And in terms of this issue that you raise in your declaration about the short duration of follow-up, you were of the view that the Gomm and Pottegard studies shouldn't have even been conducted until more time passed. Right?

A. Well, I mean, if you look at Gomm, if you count for latency, meaning that let's say the cancers that happen in the first year after follow-up, there are probably cancers that have started way before the use of the drug.

So if you exclude those, they only have maybe about a year of -- or two years of follow-up. That is inadequate. Pottegard had, you know, a bit longer of a follow-up, but Gomm had much less.

Q. Right. And what you told us is you should wait until you have adequate follow-up. And these studies that had three, four, four-and-a-half years, shouldn't have even been done

until you had adequate follow-up time. Right?
A. Well, I mean, optimally that's what you want. Whether you should have waited and not have done this study, again, my concern -- my other limitations that I brought up and you also alluded to by pointing to my letter is the misclassification and the measurement error and other limitations, all of which collectively led me to giving them a lower weight. It wasn't just the follow-up issue.
Q. Under -- sorry, sir.
A. Yeah, that's it.
Q. Okay. But on this issue, when we asked you about this issue, this follow-up issue --
A. Uh-huh.
Q. -- you said these studies shouldn't have been done because there just simply isn't enough data. Right?
A. Is this -- are you going back to my deposition again, or --
Q. Yes. Do you want me to show it to you?
A. Please.
MR. VAUGHN: Doctor, I think you might have a transcript as well, so when she shows it to you, if you need to review other pages for the full context, please feel free to take your time.
BY MS. BROWN:
Q. We're going to go to the first day, Doctor, to page 172.

And we're going to go to line 3.

All right. And you were asked this question: And with respect to just discussing the limitation you have identified of time to follow-up, you understand these products were on the market only relatively recently, so approximately 2014 and 2018. There's not at the moment an opportunity for any longer follow-up?

There was an objection, and your answer was: Yes. I mean, that's the problem. But that doesn't take away from the fact -- I mean, if you can't do this study, you shouldn't do it. You should wait until you have adequate follow-up. You cannot do sort of a -- you cannot disregard an important part of this study design, which is adequate follow-up, because there just simply isn't enough data. I mean, they could have waited until more data is accumulated before they actually did this study.

That was your testimony in August of this year. Right, sir?

A. Yes. Can you please go maybe a bit higher up right before this?

Q. Yeah, absolutely.

This Q and A is sort of going to an issue that we talked about earlier, right, sir, the control group?

A. Uh-huh.

Okay. So can you rephrase your question again, please?

Q. Sure. I just want to confirm that the testimony we looked at about whether or not there was enough data available today for the Gomm and Pottegard study design, if this testimony I read to you was accurate?

A. Yes. I'm basically saying the longer or the more time you have, the better. And perhaps if the follow-up time that you have is really short, like Gomm, perhaps it's better to wait until more data is accrued and collected to do this study.

Q. Doctor, the final area of inquiry for you today has to do with the methodology that's at issue in your declaration.

This is not the first time that you have served as an expert witness for plaintiffs' lawyers in litigation. Right?

MR. VAUGHN: There's no methodology in his declaration. He's correcting how he was taken out of context, and I don't understand how him being a plaintiffs' expert previously has to do with his declaration.

MS. BROWN: May I be heard, Judge?

THE COURT: Yeah. What is the methodology that's contained in the declaration?

MS. BROWN: Yes, sir. The methodology I think is critical, Judge, because what the declaration deals with is how based on the doctor's methodology, he has decided to give two studies less weight than others in his Bradford Hill analysis. And the fact is, Your Honor, is that he's done this

before and his opinion has been excluded because that methodology is unreliable. And that's what I want to ask him about.

THE COURT: He's done --

MR. VAUGHN: His declar- --

THE COURT: Excuse me. He's done what before?

MS. BROWN: He's performed a Bradford Hill analysis by disregarding certain information, and that has been found unreliable, and his general causation opinion has been excluded on that basis, Your Honor.

THE COURT: And when and where was that?

MS. BROWN: That was in the Fosamax case, Your Honor, in the Southern District of New York. And the opinion that excluded his methodology on general causation is from July 27, 2009.

THE COURT: Do you cite that in your brief?

MS. BROWN: Your Honor, I am very new here, and I do not believe so, which is why I was going to ask the doctor about it.

THE COURT: So you've never raised this before?

MS. BROWN: I'm hoping somebody on the line might be able to step in and help me on this. I apologize, Your Honor, I've only been involved in the case for a few days, but I do not believe this has --

MR. VAUGHN: I'm unaware of it being raised.

MS. BROWN: -- been part of the briefing.

THE COURT: It's not part of the briefing that I can recall or I can find at the moment.

The whole purpose of this was really not to get into new issues.

MS. BROWN: I --

THE COURT: I went to some great extent on Monday --

MS. BROWN: I know, Judge.

THE COURT: -- with defense counsel about their opportunity to present everything they wanted to present, but I didn't hear a word from you or Mr. Trischler that -- about any of this.

MS. BROWN: Yeah. And I apologize. I'm brand new here. As you know, I just entered my appearance. And in looking at the supplemental declaration and understanding completely that we are to tailor our questioning specifically to that declaration, I couldn't help but see that the very same methodology led to this exclusion, and I think it's exactly on point.

I mean, there are two reasons he was excluded there: One was disregarding certain information that, you know, went the other way, as we would argue these two studies do; and two is even doing a Bradford Hill analysis in the face of not having an association between the drug and the injury, which we would argue is the same here. So the exclusions seem sort

of directly on point here, Your Honor, and --

THE COURT: Wait a minute.

You're suggesting there's no evidence of an association between NDMA and cancer?

MS. BROWN: No, Your Honor. It's between the medicine.

So I think what this Court was holding is that you would have to have established causation between the drug -- before you even do the Bradford Hill. Right? The Court in two parts -- one, the Court questioned what happened here, right, which is where you sort of give little weight to certain studies and exclude it on that basis. But, two, the Court also said, Your Honor, look, we're questioning whether a Bradford Hill under these circumstances is even appropriate where it hasn't been conclusively established that there's an association between the medicine. Right? Not the compound, not the, you know, contaminant, but the medicine and the injury.

And so on those two points, Judge, it seems, you know, kind of on the four corners here of what's happened in this case.

MR. VAUGHN: Your Honor --

THE COURT: Wait a minute, wait a minute, wait a minute, Mr. --

MR. VAUGHN: Sorry.

THE COURT: Wait a minute, wait a minute.

Yeah, I think you're correct. The Third Circuit, in order to get to causation, you have to establish association, and then you apply either the Bradford Hill principles or the weight of the evidence principles to that to give your causation opinion. Okay?

And I don't know what happened in Zoloft with this witness. I don't really care.

But are you suggesting that the plaintiffs in this case have not established the association element of that requirement?

MS. BROWN: Yes, Your Honor. In terms of the medicine, I am. So I understand they're relying on sort of general studies, food studies, occupational studies, about the compound itself. But I would suggest, Your Honor, because dose is so important, Your Honor, that they would -- before they even get to a Bradford Hill, they would have to establish that at this dose, these trace levels are generally capable of causing the nine cancers.

THE COURT: Ms. Brown, that's very clever, but perhaps you can explain to me why there was the recall by all these government agencies if there's no association.

MS. BROWN: I understand, Your Honor, completely. And I would suggest, though, that regulatory decisions like that are often not in complete concert with the law on

causation and particularly the law on Daubert, Your Honor.

And I understand out of an abundance of caution, there were actions taken by the FDA. I understand that completely. But I would suggest, Your Honor, just on the methodology, that this Fosamax opinion is enormously instructive and I think raises real questions about the analysis that this doctor did.

THE COURT: We'll set aside all the government agencies around the world who decided there's an association, therefore, we have to order a recall.

What about the statements made by the officers, employees of the defendants, the vice presidents and officers who clearly state that this stuff is a human carcinogen? That's not an association? Your clients think it is. Why is more even required?

MS. BROWN: I understand that completely, Judge. And I guess I would just say this. Like I would use, Your Honor, asbestos as an example, let's just say. Right? I mean, we would all agree asbestos is a carcinogen. Everybody agrees asbestos causes cancer. But at the same time, the EPA allows a certain amount of asbestos in our drinking water. Right? We know that everybody's exposed to asbestos. We all have asbestos in our lungs. And we know that the FDA has recalled products because of a concern about potential asbestos contamination; but we know upon further investigation, those

products don't have enough asbestos in them to cause cancer.

So I would just suggest to the Court, I completely understand, you know, the concept that this is, you know, a substance that in certain circumstances may be able to cause cancer, but I think the inquiry has to be here for this Court in this circumstance, in this medicine, could it do it? And I would suggest to Your Honor that these experts just on their own admissions haven't done that.

THE COURT: There is no answer to the question yet in science. You have two sides to this question. You have two groups of experts totally opposed to each other in this case as to what the science says, which is not really unusual, I think you'll admit, because you've been involved in a lot of cases. Right?

MS. BROWN: Yeah, Judge, a lot of cases like this with trace contamination where you've got to figure out how much, you know? I mean --

THE COURT: No, I get it. But that's the fun of being a lawyer, because who knows. I mean, you take it to a jury, and the jury says, well, I know --

MS. BROWN: I know.

THE COURT: I think that what you're trying to --

MS. BROWN: Yeah. There is like an initial -- you know, we got to obviously get past -- they have to get past you, Judge, as the gatekeeper. Right? And I would just

suggest to the Court that means they have to be able to show in the way that these plaintiffs were exposed, can it generally cause cancer? And that requires an analysis that I would submit hasn't been done here, and that, you know, the Fosamax court excluded on those very grounds.

THE COURT: Well, I don't see any parallel between this and the Fosamax case, because I think -- I really do believe that the association element has been clearly demonstrated, both through all the action by the government agencies and through the words of the defendants themselves.

So now we're at weight of the evidence, and now we're its -- where it gets tricky, Bradford Hill. And the jury's going to have to hear all this argument, and, you know, you're going to -- defense is going to cross-examine vigorously the plaintiffs' experts. And they're doing a great job so far of doing it, and the jury's going to have to determine.

But I don't see any basis that this Fosamax case should at all influence what I think of the declaration of this witness. So let's move on, please.

MS. BROWN: Okay. Understood, Your Honor.

I think with that, Your Honor, I can conclude.

Could I submit the opinion to the Court, though, for consideration, the Fosamax --

THE COURT: Just give me the citation. I'll look at it, then, you know --

MS. BROWN: Okay. Terrific.

Your Honor, it's In re: Fosamax Products Liability Litigation, 645 F. Supp. 2d 164 (2009). And I would direct the Court to -- at 187 is where the discussion of Dr. Etminan begins.

THE COURT: Okay.

MS. BROWN: I appreciate it, Judge. Thank you.

And thank you, Doctor, for your time. I don't have any more questions.

THE WITNESS: Thank you.

THE COURT: Mr. Vaughn, did you want to ask any questions?

MR. VAUGHN: Yes, if that's okay.

THE COURT: Sure.

MR. VAUGHN: Are we good to start now?

THE WITNESS: Sure.

MR. VAUGHN: You're on mute, Judge, Your Honor.

THE COURT: Ms. Brown, when do you have to leave? It's almost 2:00.

MS. BROWN: I just had my paralegal say -- tell me when the judge gets on. So I think I'm okay for right now. We have --

THE COURT: If you're going to start at 2:00, then let's not, you know, interrupt in the middle of a question.

How long are you going to be on with this other

judge?

MS. BROWN: I just am going to be on, Judge, for 30 minutes or less, if I can, and if that would be okay, with your indulgence.

THE COURT: That's fine.

Who is this judge?

MS. BROWN: It's Judge Licht in Rhode Island, Your Honor. I have a case set for trial up there in the spring.

THE COURT: Okay. All right. Well, then why don't we break till 2:30.

MS. BROWN: I appreciate it, Your Honor.

THE COURT: And we'll come back on at 2:30, and we'll go from there. Okay? Thank you.

MS. BROWN: Thank you very much, Judge.

Thanks, everyone.

(Recess at 1:56 p.m. until 2:32 p.m.)

THE COURT: Go ahead. Let's get started.

CROSS-EXAMINATION

BY MR. VAUGHN:

Q. Dr. Etminan, what was the purpose of your declaration?

A. The defendants had brought up a few issues regarding my report, so that's what I tried to clarify, some of those issues in my declaration.

Q. And what were you trying to clarify exactly?

A. That I had disregarded the valsartan-specific studies,

mainly the studies from Gomm and Pottegard.

Q. And did you disregard the studies, Pottegard and Gomm?

A. I did not. I allocate two pages of my report to each study. I summarized the study design and the study findings and then provided line-by-line detailed discussion of the methodology and its limitations.

MR. VAUGHN: Thank you, Dr. Etminan. I have no further questions.

THE COURT: Ms. Brown, do you have any questions on that?

MS. BROWN: I do not. Thank you, Your Honor.

THE COURT: All right. Well, look.

I did look at the Fosamax case. First off, the ground wasn't raised in the motion to exclude the doctor's opinion. But having looked at the Fosamax case, I'm not impressed.

He was permitted to testify on the limitation of certain clinical trials. But the problem there in that case for this witness was, as the court noted, there really wasn't any associational evidence and there was no methodological reason for him to have gotten to Bradford Hill without first the association of evidence.

Here that's completely different. As I've said -- and I understand Ms. Brown's point that there is no strong -- there is no association evidence as to the particular

prescribed medicine that was contaminated and the ultimate tumors that are formed. In fact, the two studies which we've spent a lot of time talking about seem to indicate that there's not a lot of strong associational evidence, although they do indicate an increased risk of certain cancers.

Anyway, I've already decided that there is strong associational evidence, so there was no reason why Dr. Etminan could not get to the Bradford Hill factors in this case. So I don't think the Fosamax case is terribly helpful.

All right. This is what I want to do, folks. I want to take just a couple more minutes, give me about ten more minutes. And then I want to come back on the record and talk about some things. Okay? So give me ten minutes. Thank you.

MS. BROWN: Thank you, Your Honor.

THE WITNESS: Can I be dismissed or --

THE COURT: Yes, Doctor. We're done. Thank you.

THE WITNESS: Thank you. Thanks, everyone.

(Recess at 2:36 p.m. until 2:48 p.m.)

THE COURT: Okay. Anybody wants to join back in and listen, I want to go back through some things with you at this point.

Ms. Mitchell, are you ready?

All right. I want to go through some of these witnesses, these experts, and tell you my decision on your motions.

Let me first thank you for the extraordinary work you did on these motions. I mean, you put in a heck of a lot of time and effort. A heck of a lot of thought went into these things. It was very illuminating in many instances.

I follow up what I said on Monday, that I think some of you may have misunderstood my role in all this, but we'll get into all that.

The declarations I think were helpful but not dispositive.

Let's start with Dr. Lagana, who, by the way, said something very interesting during his testimony today, which may be obvious, but it needed to be said. And that when these experts are determining which studies they want to rely on and which studies they don't want to rely on, there is an element of human judgment involved in this.

And I think that's true of every expert on both sides of this case. I don't think that's objectionable at all.

But anyway, the first issue that we dealt with and you dealt with in your motions to bar his testimony about this null hypothesis, he explained in his certification, particularly starting at paragraph 3, that he starts with certain assumptions when he's doing a differential diagnosis of a patient, and indeed, that is good medical practice. And he talked about it.

And I think we all know that if a doctor prescribes a

medication to someone and they come back to the doctor complaining of certain side effects and the doctor knows that that medicine has those known side effects, there is no reason why she should have to start with a null hypothesis. And I think it's pretty clear that what he was talking about applied only to the clinical practice of medicine.

Now, defendants also complained that he uses different methodology than he does in his job as a pathologist, and they point to the Benicar case and the use of slides. But he explained all that. And I think that Benicar really is not a good comparison. And Benicar slides had to be examined in order to diagnose the specific injury that was involved, because if you didn't have a specific injury, you couldn't file suit in that case.

Furthermore, examination of the slides in the Benicar case yielded no information whatsoever on the cause of those diseases. Just as would be here, I don't see how in a general causation opinion examination of any slides of these tumors is going to tell you how they were caused.

Defendants also raised the issue of, again, which studies he relied on, which studies he didn't rely on, why didn't he give certain weight to some studies, why did he give so much weight to other studies. And this is a complaint that both sides have as to every single expert in this case. And this is about the cherry-picking of the data. But really

that's what experts do. They look at the data, they decide and they express their reasons why some data is more important at arriving at their opinions than others.

So long as they explain how they come to their opinions, and so long as they attempt to explain why they didn't think contrary data is not relevant to their opinion, then that's not objectionable.

His opinion about increased risk is not controversial. It's not an ipse dixit assertion that he makes. I think you also need to look at the whole picture. Like I said, like the Third Circuit has said, we're not looking for better experts and better opinions, we're just looking at what's there and whether or not methodology was followed.

And what he did in this is he employed the usual research in finding and discussing relevant animal studies, observational studies and other data. He does discuss the contrary data. Noting the associational evidence, he moves on to the Bradford Hill Principles to render his conclusion of general causation. He has an opinion as to how these chemicals can cause cancer. The alkylating agent or the activation, as he explains, of oncogenes. Accordingly, I find no problems with his methodology, and the motion to bar his testimony is denied.

Dr. Panigrahy, I think there was a misunderstanding

by defense counsel here as to what he was talking about in his certification, and that's the concept of bioavailability. According to him, bioavailability is not dependent whatsoever on saturation. They're really not related, except if you reach a total saturation point, then the bioavailability increases to 100 percent. But he's very clear that there is NDMA that escapes through the liver into the bloodstream, and he relies on animal studies to do that.

Now, I've talked about animal studies. We all are aware that there are certain shortcomings of animal studies. But folks, that's what researchers use, particularly where you can't do human studies, as you can't do here.

And I think it's important that we remember, and I referred to this earlier about the words of some of the defendants and some other scientists about how this substance, it can be dangerous, how the substance can lead to cancer. I think the associational evidence is certainly sufficient to get this to the jury.

Dr. -- Mylan's senior director Lance Molnar testified about the categorization of nitrosamines by the regulatory bodies as -- he talked about non-threshold or not subject to the presumed acceptable thresholds set forth in applicable guidelines and set forth in EMA, et cetera. And that means a single molecule could be detrimental. And that's from his deposition.

Here as to Panigrahy, the defendants complain about the heavy reliance on Hidajat. Of course there are limitations. I've talked about that already.

But this is a jury question. The jury is going to have to determine which of these studies they think are important and which are not for the reasons that you're going to illustrate to them.

Defendants complain that the daily accepted intake level is an improper proxy for general causation. The problem is, once again, that the various government agencies have determined that NDMA is a probable carcinogen. These public health guidelines alone of course cannot establish general causation, but he never claims that they do.

He has an opinion about the development of cancer in downstream organs, how much NDMA survives the liver. And again, it's based on animal studies and based on these studies that show, for whatever reason, the larger the animal species, the greater the amount that escapes through the liver.

There's nothing new about extrapolating from animal studies, particularly here where apparently every species of animal seems to have been studied and seems to have developed cancer.

He uses the same methodology he would in his own research, and of course the jury doesn't have to believe anything he says, but that's up to them. So the motion is

denied.

Etminan, the most recent witness, defendants complain that he does not calculate or consider baseline NDMA or NDEA exposure. And that, frankly, is a weakness in all the reports that I've seen. Based on the exposure apparently meaning that you have to measure what people eat, what they drink, where they live, what they breathe; all contributing to baseline exposure. That's not fatal, because again, the methodology Dr. Etminan uses is sound.

And again, the defendants raise the issue of, you know, he raised -- he relies on some studies and not others. And in his declaration and in his testimony today, we spent a lot of time talking about why the Gomm and the Pottegard studies weren't terribly helpful in arriving at his opinions.

The jury may reject that. They're free to reject that, and you're free to argue to the jury that they have to reject that.

Defendants complain of his reliance on Hidajat. And they say, well, you know, he didn't apply the same standards. Well, he did, as far as I could tell, apply the same standards as to why he accepted some and not others. I'm not going to be the one to determine whether these are good studies or bad studies.

The defendants raised the issue that he misapplies his own criteria, things of that nature. He did examine a

significant number of studies. Again, he provides an explanation as to why some are noteworthy and some aren't. Again, this is a jury question.

Defendants complain he misapplies Bradford Hill. This again is a disagreement as to what studies are significant and what aren't, particularly the Hidajat study.

Again, you need to focus on the big picture, the whole picture, what has he done in this and what has he not done. We're not trying to find a better expert report, we're just trying to find out if he follows accepted methodology, which I find that he has.

Defendants are correct, though, about the NDEA. There's very little on that. And there's -- he can express an opinion as to the association between NDEA and pancreatic cancer because that's the only data apparently that's available, but he cannot express an opinion as to NDEA exposure in esophageal, stomach, colorectal, liver, lung, bladder or prostate cancer. So the motion is denied except as to those cancers.

I'm going to go through some of the ones who have not testified because there's no point in waiting on that, because that's not going to change.

Hecht, Stephen Hecht, H-E-C-H-T.

This is again another complaint about failure to consider dose threshold for his conclusion that NDMA and NDEA

cause cancer at the levels present in this valsartan-containing drug. But the FDA and other regulatory agencies have already done threshold level calculations. And he's entitled to rely on those. Again, the jury doesn't have to agree, but he's entitled to rely on those.

There's the issue of extrapolation from animal studies. I've spoken about this. There's no reason to continue that discussion.

I understand that the point being made by defense counsel about the high doses of these substances that are force-fed to these animals, but I think the experts will tell you and have told us that's just the way they do the test, primarily because of the relatively short lifespan for these animals. And the FDA and the EMA and all the regulatory agencies rely on these animal studies.

Defendants complain that Hecht didn't do any independent testing. Well, nor did most other people in this case. They complain there's no definitive study that shows that these drugs, these contaminants cause -- any of these drugs cause cancer. Well, that's true. But again, it's a difficult proposition, because you cannot do any human clinical studies because of the danger of this drug.

And remember Daubert. The opinion expressed does not have to be generally accepted in the scientific community. What has to be accepted is the way you go about doing your

research.

The methodology he uses is the same as everyone else. He examines all the studies that are available, he explains why he thought some were not terribly helpful or relevant and why some were. The jury will have to straighten this out.

And there's an issue about background exposure. He acknowledged that. Others did also, did not take into account background exposure. But again, you need to focus on the whole picture, what was done and what wasn't done. These weaknesses in all these experts are certainly going to be fertile ground for counsel in examining and cross-examining these experts.

What he does do is refer to the various government agencies and their findings. He analyzes the studies. He discusses the defendants' own statements and explains why he believes the contrary studies, Pottegard, Yoon, everyone else, are not terribly helpful. Accordingly, the motion is denied.

David Madigan. Defendants complain he does not give an opinion on general causation, and indeed he does not. He's only going to be offering opinions on the strength of association evidence, which as we know is the beginning of the road that may lead to causation by applying Bradford Hill or weight of the evidence.

Defendants, interestingly enough, cite cases in which Madigan's been barred from testifying as to certain opinions.

And one of them is the incretin, I-N-C-R-E-T-I-N, case, which interestingly is going to be argued Monday in the Ninth Circuit. I'm not sure whether the Madigan issue has been raised in that because I didn't read the briefs in that case. But that might be interesting to tune in.

But the incretin case really doesn't apply, because in that case the court noted that there were absolutely no studies or animal experiments or clinical trials or observational studies or any analysis that a single researcher or organization had up to that point concluded that incretin caused pancreatic cancer. And indeed, the FDA had spent a decade studying it and had consistently said that there was no causal association even between incretin and pancreatic cancer.

This is entirely different from our case here. We have numerous studies that make the argument and numerous government agencies who found that these substances are probably carcinogenic.

In incretin, Madigan also had an updated history for it, and he had changed his methodology and the opinion he was going to offer. Actually, probably I would have barred anyway but not on Daubert grounds because I didn't think it was very relevant anyhow.

But anyway, in Vioxx he was permitted to express his opinion on the statistics.

And the other cases they rely on I don't think are controlling this question.

The defendants claim that it's really an epidemiological opinion and of course he's not an epidemiologist. He's a statistician. But all epidemiological conclusions are based on statistics. Of course metaanalyses are only as good as the underlying data. Distortions do exist. But that doesn't mean they aren't recognized in the scientific community. Many disciplines, sociology, you name it, use metaanalysis. They are recognized in scientific circles as having some value.

Defendants claim he only reviewed studies that were hand-picked for him. But he uses studies cited by Etminan, who did a thorough review, which Fryzek, the defense expert, comments favorably on.

The defendants' claim about his conclusions from Hidajat, I don't need to further comment on that.

There's the issue of dose, timing, duration of individual exposure, and the defendants rely on the Hoffeditz, H-O-F-F-E-D-I-T-Z, case from the District of New Jersey about the single exposure, single molecule theory. And indeed, that case did condemn that.

But it was applying Pennsylvania asbestosis law in that case. And under Pennsylvania law, you had to prove that the exposure was frequent, regular and proximate. And the

testimony that each and every exposure of asbestos is causative of mesothelioma, it was not permitted. But that was Pennsylvania law about asbestos. That's not really the law here. And incidentally, the expert was permitted to testify, because the amount of exposure was significant.

Defendants further complain he makes an impermissible inferential leap from dietary and NDMA occupational exposure to pharmaceutical exposure. Again, how and why experts rely on certain studies and not on other studies is a jury question.

We raise the issue again about NDEA because you only have the Zheng, Z-H-E-N-G study. Madigan does say that NDEA and NDMA are similar, however, he provides no explanation as to how that is so, and he provides no analysis of bladder, breast, kidney, pharyngeal, or uterine cancers. Consequently, he will not be permitted to testify about NDEA. Otherwise, that motion is denied.

Turning to some of the defense experts who are not going to be giving testimony, John Flack, F-L-A-C-K, plaintiffs point out that he has no experience with NDMA or NDEA, has no background in toxicology or oncology or cancer research and doesn't consider a lot of the relevant literature. He acknowledged in his deposition that his opinion would be quote, blasted, B-L-A-S-T-E-D, in the academic world.

I find he does not consistently apply any recognized methodology to his opinions, but he does have experience in treating hypertension. And therefore, he is competent and capable of testifying that hypertensives have a higher incidence of cancer, and obese hypertensives, an even higher risk of cancer because of these underlying conditions. Otherwise, the motion is granted and he'll be barred from testifying about anything other than these two.

Janice Britt, B-R-I-T-T, this one is simple. Although Daubert and other cases hold that the conclusions don't necessarily have to be supported by general acceptance in the relevant scientific community, the methodology must be acceptable.

The problem for Britt is that the methodology she uses, EBT, is not recognized in the scientific community as a standard used by toxicologists to weigh dangers caused by any substance. She didn't even use the EBT methodology that she describes. So that one's easy, and that motion to strike her opinion is granted.

John Fryzek, F-R-Y-Z-E-K. I have to comment that there are all kinds of interesting cross-examination materials here: The employment discrepancies, the resume discrepancies, the alleged professorships at Vanderbilt and elsewhere that apparently weren't so, the absolutely baffling billing discrepancies in this case and in the Welding Rod MDL.

But this is all ammunition that you can use for cross-examination, and we'll see what the jury says about it. It has nothing to do with the issues that I need to decide.

His methodology is he says that he did a systematic literature review based on certain standard techniques. He looked for studies that described the risk of cancer with exposure to valsartan-containing drugs, and he looked for studies that described the risks of cancer with dietary exposure to NDMA and NDEA. By definition and by his search terms, he probably missed some.

But his methodology in and of itself is not objectionable. He says that his search yielded 1,884 results on these studies. He reduces that to 109 articles using, he says, his criteria. He added 8 by a process I don't really understand. But that leaves 117 which he examined in full. He eliminated 92 for various and sundry and good reasons, so he ends up with, you know, a couple dozen. And of course, like all defense experts, relies heavily on Pomm, P-O-M-M, Pottegard, P-O-T-T-E-G-A-R-D, Al-Kindi, A-L-K-I-N-D-I, and Yoon, Y-O-O-N.

He reviews the same studies as plaintiffs' experts which plaintiffs show -- claim show a connection between NDMA and various cancers, but he disagrees with those conclusions. He criticizes the plaintiffs' experts in much detail and the studies they rely on in an attempt to distinguish them. For

having used the basic methodology, that motion to bar his testimony is denied.

Lee-Jei Wei, it's L-E-E dash J-E-I, last name W-E-I. I'm sure I'm not pronouncing that correctly. I assume that the sole purpose of his testimony is to refute Madigan's findings and the data that Madigan relied on.

The plaintiffs raise some interesting points, which probably deserve some comment. The witness seems to have used a template from other cases he had written reports on. He spends pages discussing human clinical trials which have absolutely no relevance to this case.

And as to his methodology, his criticism of metaanalysis, again, a technique used in all scientific disciplines, results in no metaanalysis passing his test. He states no recognized methodology that can lead one to this result, thus, he will not be permitted to testify about metaanalysis.

There's no basis for any opinion he has on lifetime cumulative exposure, LCE. He's never done any calculation, can't even approximate the amount of NDMA in these medicines and doesn't have any idea how Madigan calculated it. Thus, the basis for his criticism of Madigan's calculation is unknown, and he won't be permitted to testify about that.

He also -- it's hard to tell -- it's hard to tell about a lot of what he says. He's hard to follow in his

deposition. And I'm sure plaintiffs are going to have fun cross-examining him on some of the things he said about, you know, society being better off, et cetera, et cetera. But to the extent he's trying to express opinions that exposure to NDMA does not cause cancer, that will be prohibited, because as best as I can determine, the only basis for that opinion is, well, Madigan makes the connection and Madigan is wrong, so therefore the opposite must be true.

So he's not going to be permitted to offer any opinion that exposure to NDMA will not result or increase the risk of any cancers. Other than that, he has methodology, he cites to certain techniques he says Madigan should have used and should have followed, and he's permitted to testify about those things.

All right. The only two we have left. And plaintiff apparently wishes to question or -- Bottoroff and Johnson if they want.

Have we made arrangements for a time to start on the 15th? Or are you still working on that, guys? What's going on?

MS. LOCKARD: Your Honor, we can have our witnesses here, you know, if you want to start around the same time, 9:30. We are -- we have worked it out so that we can have Dr. Johnson and Dr. Bottoroff both on the 15th, if that still works. So we'll plan to proceed at this point. I don't know

exactly who will be first, but I can let Your Honor know when we know that.

THE COURT: That's fine. That's great.

I think the plaintiffs need to decide whether they're going to go through with the exercise first. But anyway, if they do, I'll be here.

All right. I think that concludes what we're doing today. Thank you, everybody. Have a great evening, and we'll see you in a couple of weeks.

RESPONSE: Thank you, Your Honor.

(Proceedings concluded at 3:18 p.m.)

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I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

/S/ Ann Marie Mitchell, CCR, CRR, RDR, RMR
Court Reporter/Transcriber

4th day of March, 2022
Date